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JANUARY 1941

THE SEX HORMONES AND THE
ENDOCRINE BALANCE*

*The Middleton Goldsmith Lecture of
The New York Pathological Society*

W. CRAMER

Research Associate, Barnard Free Skin and Cancer Hospital, St. Louis

ALLOW me to thank you for honoring me with the invitation to give the Middleton Goldsmith Lecture. Your society is, as far as I know, the oldest pathological society in this continent and one of the oldest, if not the oldest pathological society of the world. It will soon be able to celebrate its centenary. It was founded in 1844 and Middleton Goldsmith, whose bequest established this lecture, was one of its founders together with Lewis A. Sayre and John C. Peters.

When this society was founded, Virchow, who is generally acclaimed as the father of the science of pathology, was twenty-three years old, Pasteur was a year younger, and Lister was a boy of seventeen. New York, where the three founders were young practicing physicians, was at that time a small city ending at what is now 14th Street. Its medical facilities consisted of one college, one hospital, and three dispensaries.

* Given October 4, 1940 at The New York Academy of Medicine.

How did it come about that three young doctors in this environment conceived the idea of founding a pathological society? It is probable that the inspiration came from Vienna though indirectly Peters had returned from Vienna, where he had come under the influence of Rokitansky, that queer personality who spent his whole working life in the dead house. He is said to have carried out about one thousand autopsies every year for a period of forty years. He and his clinical colleague, Skoda, were then the leaders of the Vienna school, whose ambition it was to establish medicine as an exact science by testing the correctness of every diagnosis by an autopsy, if the patient provided the opportunity. Peters had probably been infected with Rokitansky's enthusiasm for the study of morbid anatomy as the means of advancing medicine, and this bore fruit in the foundation of your society.

But whether the seed that flowered here in little old New York was planted in Vienna or not, to have recognized at that early date the fundamental importance of pathology for the advancement of our knowledge of disease and to have started in this then remote city and without academic support a medical society to be devoted to the exclusive study of a branch of medicine which was just being born in Europe, gives evidence of a far-sighted optimism, so characteristic of this country, which compels our admiration. For this, the names of Middleton Goldsmith and his two co-founders, Sayre and Peters, should be gratefully remembered, and there could not be a more suitable opportunity than this lecture.

In this lecture I wish to lay before you a conception of the inter-relationship of the endocrine glands which reveals them as forming functionally one system consisting of a number of units continuously interacting with one another. It is a conception which, while introducing some surprising physiological connections between the different glands, has a special bearing on the still very obscure question of the factors determining the functional activity of the endocrine glands in health and on the even more obscure disturbances of their functional activity as seen by the clinician and the pathologist in disease.

Our interpretation is based on a physiological axiom, which dates back to Claude Bernard, that in a highly differentiated organism the functional activity of the various organs is correlated in such a way as to keep the internal environment constant. More recently the same idea has been expressed by Bordet: "Life is the maintenance of a

balance which is incessantly being disturbed" In this country Cannon has pursued this idea and given to this conception the name "Homeostasis" Cannon as a physiologist emphasizes the maintenance of the balance, Bordet as an experimental pathologist is impressed by its incessant disturbance In the maintenance of this balance, as in its disturbance, the endocrine organs play a part of outstanding importance The internal environment is subject to disturbances as a result of changes in the external environment, such as changes in temperature and the intake of food and also as a result of the activity of the organs, such as muscular movement and, what is of special interest in its bearing on the problem under discussion, the activity of the endocrine glands themselves It will be easier to follow the argument if I state our conception now and present the facts and observations which led me to it subsequently It is, briefly, to regard all the divers endocrine glands as forming one system, in which the individual glands are functionally correlated with each other in varying degrees This correlation depends upon the direction in which the individual hormones secreted by the endocrine glands affect the internal environment There are glands the functional activity of which produces a disturbance in the same direction, for example, the thyroid and the adrenal medulla Such glands are synergists There are others which when functionally active, produce changes in opposite directions, for example, the islets and the thyroid are antagonists, and so are the islets and the adrenal medulla In the normal resting organism the internal environment is maintained at its normal level by a balance between the functional activity of the different endocrine glands If one of these glands is primarily stimulated to functional activity there results a disturbance in the internal environment In order to restore this to the normal there is a secondary compensatory response in other endocrine glands, which may be of two kinds the antagonistic gland may show a compensatory increased functional activity, while the synergistic gland may be inhibited This general pattern is indicated in Table I, in which increased functional activity is indicated by a plus sign, inhibition or dysfunction by a minus sign When the primary change in an endocrine gland is an inhibition or a dysfunction, produced either by disease or by experimental interference, the secondary compensatory response in other endocrine glands manifests itself in the reverse manner that is, the antagonists are then inhibited or the synergists are stimulated to increased functional

TABLE I

Primary Change in One Endocrine Gland	Compensatory Change in Antagonist Synergist	
+	+	—
—	—	+

activity or both groups of responses occur together

It is by this arrangement for the maintenance of the internal environment that the functional activities of the divers endocrine glands are interrelated with each other in such a way as to form one system. It may be added that the term antagonist does not imply that all the effects of one hormone are neutralized by the action of its antagonist. The antagonism is only a partial one, and the same is true for the synergism between two glands.

The relationship of the adrenal medulla, the thyroid and the pancreatic islets, which I had investigated in my earlier work¹ offers a good example. The adrenal medulla and the thyroid gland are synergists. They act on the glycogenic function of the liver and on metabolism generally in the same direction, stimulating it. They are stimulated by the same changes in the internal environment, such as exposure to cold, and by the same chemical substances, such as tetrahydronaphthylamine or the toxins of certain bacteria, resulting in the production of fever. Both glands are inhibited in their functional activity by heat. These facts have been established by the method of what one may call functional histology. Functional histology depends on a technique which reveals the functional state of endocrine glands in a direct and incontrovertible manner. It has proved its validity by demonstrating for the first time that the thyroid and the adrenal glands are intimately concerned in the heat regulation of the body and in the etiology of fever.

The effect of insulin, on the other hand, is antagonistic to both thyroxin and adrenalin. It inhibits the glycogenic function of the liver. The antagonism is very evident in relation to the change produced in one feature of the internal environment, the blood sugar. Insulin produces a rapid fall of blood sugar, adrenalin a rapid rise, while thyroxin

produces an increased supply of blood sugar which is oxidized *pari passu* with the increased supply. The fall of blood sugar produced by an injection of a moderate dose of insulin elicits a compensatory activity of the adrenal medulla which by secreting adrenalin tends to restore the blood sugar to normal. The secretion of adrenalin under this condition, which can be demonstrated by the method of functional histology, is not due to a direct stimulating effect of insulin on the adrenal medulla. For, if insulin is injected together with glucose, so that the fall of blood sugar is avoided and the internal environment is not disturbed, the secretion of adrenalin does not occur. We have here an example of one of the conditions which stimulate the functional activity of an endocrine gland, in this case the adrenal medulla, as a secondary compensatory response to the disturbance of the internal environment produced by the functional activity of its antagonist—in this case the pancreatic islets.

The antagonism between the islets on the one hand and the thyroid-adrenal-medullary apparatus on the other can be demonstrated also from the opposite direction. Any condition which arouses the functional activity of the thyroid or of the adrenal medulla, such as exposure to cold, makes the organism more resistant to the effects of insulin and conversely anything which inhibits the thyroid or adrenal medulla, such as exposure to heat, makes the organism more sensitive to insulin. This relationship is now clearly recognized in the biological assay of insulin in mice, where it is necessary to keep the animals in a constant, warm environment in order to obtain reliable results. This argument applies also to pathological conditions involving an increase or a diminution in the functional activity of the thyroid or adrenal medulla. The increased resistance to insulin of diabetic patients suffering from Graves' disease or from septic infections which was predicted in our conception has been confirmed clinically.

The interrelationship of these three glands with reference to the glycogenic function of the liver, is summarized in a diagram published twelve years ago in my book ¹

Since we are discussing the functional interrelationship of glands of internal secretion, it is appropriate to recall the fact that the conception of "internal secretions" was invented by Claude Bernard to describe the glycogenic function of the liver. In coining this term, "internal secretion," he wished to emphasize the autonomous glandular

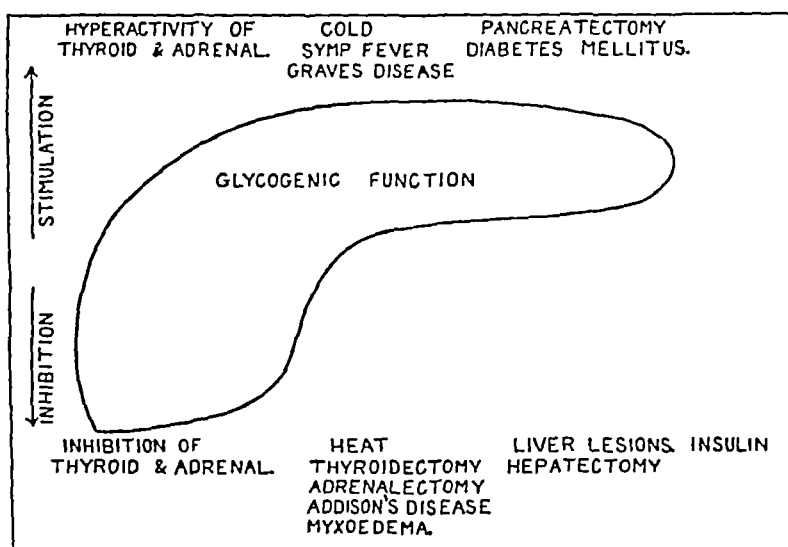


Fig 1—Interrelation of thyroid, adrenal and pancreas in the glycogenic function of the liver

nature of the glycogenic function of the liver which functions irrespective of the amount of carbohydrate ingested in the food, and even irrespective of the amount of glycogen present at any given moment in the liver, as opposed to the alternative interpretation of this function as a storage of an excess of carbohydrate in the food. The genius of Claude Bernard shines no more brightly than in this bold conception, which even today, in spite of the vast amount of work carried out on the subject, is not always fully understood.

We thus see that one of the ways, by which the functional activity of an endocrine gland may be stimulated, is as a compensatory response to a disturbance in the internal environment which may be created by the functional activity of another endocrine gland.

But in the compensatory response of an endocrine gland the typical effects of its hormone are masked partly or completely by those resulting from the disturbance of the internal environment which the compensatory response is intended to counteract. If this primary disturbance is sufficiently severe or prolonged, the endocrine gland providing the compensatory response may become extensively depleted of its load of hormone and the organism will then present a general condition, a syndrome, which will be erroneously interpreted as a dysfunction of the gland.

You will see the point of this conclusion, and of this lengthy introduction to our subject, when I describe to you the paradoxical condition induced by a continued excessive supply of the female sex hormone.² Prolonged estrinization produces in the animal slowly a syndrome which, though strikingly similar to that produced rapidly by hypophysectomy, is associated with an anterior pituitary gland showing the signs of intense functional activity. The syndrome is, as I just said, that of a dysfunction of the anterior pituitary. It closely resembles the syndrome of Simmonds' disease. When the estrogenic hormone is applied continuously over long periods it is found that every endocrine organ in the body is affected to a greater or smaller extent. In some of these organs it can be seen with the naked eye that they have undergone a change. In addition, the organism as a whole is profoundly affected. If young mice are used they are found to be stunted in growth, emaciated, in males the testes are so atrophied that they are difficult to find and if examined histologically spermatogenesis is absent. The thyroids are pale and small, the islets of Langerhans are greatly enlarged, there is an extensive and specific degeneration in the adrenal cortex, the thymus is completely atrophied and the lymph glands are smaller than normal. In short, the picture presented by these estrinized animals is very similar to that seen after hypophysectomy. But, and this is the paradox, if the pituitary is examined the anterior part is found to be deeply congested and greatly enlarged. The enlargement may be so irregular as to be called adenomatous. Histologically there is always a marked diminution in the number of the acidophile cells in the anterior part, and they may even be completely absent. In its extreme forms the condition may therefore be called a chromophobe adenoma.

Since Horning and I described this phenomenon it has been confirmed by a number of observers, who have interpreted it by saying that the estrogenic hormone inhibits the anterior pituitary. Their argument is that the anterior pituitary secretes a hormone which promotes growth. In estrinized animals growth is arrested. Hence, they argue the estrogenic hormone inhibits the anterior pituitary. But this conclusion has been drawn without examining the gland. Even a casual inspection, with the naked eye, of the pituitary after prolonged estrinization, showing a greatly enlarged and deeply congested anterior pituitary, should be sufficient to cast some doubt on such an interpretation.

The method of functional histology which reveals that the secreting cells have discharged their specific hormones, confirms the conclusion that the estrogenic hormone has stimulated the anterior pituitary to continued functional activity as a compensatory response to restore the disturbance in the internal environment produced by the effects of the continued excess of the female sex hormone

The two important points in this argument are (1) *the anterior pituitary is stimulated and not inhibited by the estrogenic hormone*, (2) *the anterior pituitary secretes a hormone antagonistic to the estrogenic hormone*

The correctness of this conclusion can be verified by an experimentum crucis.³ If the activity of the anterior pituitary is a compensatory response to estrinization, the hormone or hormones which the anterior pituitary secretes should be able to antagonize the effects of the estrogenic hormone. That is the case. If certain hormone preparations from the anterior pituitary are injected simultaneously with the application of the estrogenic hormone, many of the effects of the latter are abolished or greatly diminished: there is no arrest of growth, no emaciation, no atrophy of the gonads, no congestion, and only a slight enlargement of the anterior lobe, and the chromophile cells retain their secretion. Only the degenerative change in the adrenal cortex cannot be prevented by the pituitary extracts. It is probable, therefore, that the adrenal cortex responds directly to the estrogenic hormone, while the changes in growth and in the gonads are brought about through the intermediation of the pituitary.

I turn now to the effects of prolonged estrinization on the adrenal glands.⁴ In these glands a specific degeneration, not previously described, develops in a sharply circumscribed area, namely the innermost zone of the cortex, the zona reticularis. It begins as an enlargement of isolated cells, which acquire a brownish color with small lipoid inclusions. As these cells enlarge, several of them coalesce to form isolated brown masses, and eventually these coalesce to form a brown ring surrounding the medulla and separating it from the cortex. These masses consist of a structureless network showing a few nuclei which is impregnated with a brown material having the solubility of lipoids. Such a process of degeneration represents a reaction the opposite to that of the hyperemia and hypertrophy seen in the pituitary. While the changes in the anterior pituitary indicate a secondary compensatory stimulation, those

in the adrenal cortex should be interpreted as a secondary compensatory inhibition. On the basis of an endocrine interrelationship functioning to maintain the internal environment constant, such an inhibition as a secondary phenomenon to the excess of one hormone should be interpreted as a compensatory diminution of the secretion of a synergic hormone from the adrenal cortex.

This interpretation of a synergism between the ovary and the adrenal cortex is supported by several facts. There is, firstly, the close histogenetic relationship between the ovary and the adrenal cortex. There is secondly, the fact that both male and female sex hormones have been demonstrated in the adrenal cortex. Thirdly, there are the results of removing the adrenal glands. Mice survive the operation fairly well when it is carried out in two stages. About 50 per cent of the animals remain alive and well for many months even when there is no accessory cortical tissue visible to the naked eye such as small cortical adenomata. It was surprising to find that the mortality from adrenalectomy could be greatly diminished by estrinization if begun a few weeks before the operation, but not if started immediately after it. This suggests that the preliminary treatment with an excess of the estrogenic hormone had so altered the endocrine balance as to protect the organism against the loss of an adrenal cortical hormone. This again indicates a synergism between the functional activity of the ovary and the adrenal cortex. It was even more surprising to find that these adrenalectomized mice no longer reacted to an excessive supply of estrogenic hormone in the same way as intact animals. The striking changes in the pituitary are either less well-marked or absent. Other typical effects of estrinization, loss of weight, arrest of growth, atrophy of the testes and of the thymus, are also absent or greatly diminished, and sometimes the animals, instead of being small and emaciated, become abnormally large and fat. The thymus and the lymph nodes are then frequently enlarged and even malignant tumors of the thymus with metastases have developed. In adrenalectomized and estrinized mice, the mammae do not develop as fully under the influence of the estrogenic hormone, the testes do not undergo atrophy as they do in intact animals. Generally speaking, therefore, the *loss of an adrenal hormone* confers a similar protection against an excess of estrogenic hormone as an *additional supply of an anterior pituitary hormone*. This again shows that in relation to the estrogenic ovarian hormone the anterior

pituitary and the adrenal cortex oppose each other. That this adrenal hormone is secreted by the cortex, and not by the medulla, is shown by the fact that adrenalectomized mice in which even a very small cortical adenoma was present exhibited the same reaction to estrinization as intact mice.

In a paper published in January, 1939, we argued from these results that the adrenal cortex possesses hormonal functions synergic with those of the ovary and that this synergism extends even to the etiology of cancer of the mamma. A few months later, Woolley, Fekete and Little⁶ published the remarkable results of an experiment begun long before our publication, which are a striking demonstration of this conception. They had ovariectomized mice immediately after birth. Six months later the uterus and the mammary glands of these animals showed the atrophy one expects to find in the absence of the ovaries. But if such mice were allowed to live for a year or more, both the uterus and the mammae were found to be fully developed and 40 per cent of the mice which belonged to an inbred strain with a high incidence of mammary cancer (50 per cent in virgin females) developed cancer of the mamma. Special care was taken to prove the complete absence of ovarian tissue in these mice. But there was a striking abnormality in these spayed mice—namely, a massive nodular hyperplasia of the adrenal cortex, which in three of the animals had progressed to malignant tumors of the cortex. In those experiments, then, the removal of one endocrine organ had brought about, after a sufficiently long interval, a compensatory stimulation of another endocrine organ with a synergistic function, “thereby simulating or replacing ovarian activity,” to use the authors’ own words.

As long as we consider these diverse experimental results by themselves as isolated facts they remain curious and puzzling phenomena. But they form a coherent picture on the basis of the conclusion that the adrenal cortex secretes a hormone which acts as a synergist to the ovarian estrogenic hormone and in the last mentioned experiments of Woolley, Fekete and Little as a partial substitute. If we take the functional relationship between the ovary and the adrenal cortex as an example of two endocrine glands secreting synergistic hormones, we can express their relationship in general terms by saying that the *hyperfunction of one endocrine gland*, in this case the ovary, *induces in the gland secreting its synergist a hypofunction*, exemplified by the

brown degeneration of the cortex, while the *inhibition of one endocrine gland*, produced experimentally in this instance by removal of the ovaries, *induces in the gland secreting its synergist a hyperfunction*, exemplified by the nodular hyperplasia of the cortex. The two opposite reactions induced experimentally in the adrenal cortex—by ovariectomy on the one hand and by an excessive supply of the estrogenic ovarian hormone on the other—are both compensatory phenomena tending to correct two opposite disturbances in the endocrine balance in opposite directions.

In connection with the observation that after adrenalectomy the thymus fails to undergo atrophy under the influence of the estrogenic hormone, it is necessary to mention briefly the effects of adrenalectomy alone. It was found that in adrenalectomized animals the thymus persists or rather regenerates and the lymph nodes are enlarged. In view of the fact that our knowledge of the functions of the thymus and of the factors controlling this organ and the lymphoid system generally are very scanty, this demonstration that the thymus and the lymphoid system are under endocrine control is important. On looking through the literature I find that this effect of adrenalectomy has been observed 15 years ago here in New York, in a convincing series of experiments, by Marine and his collaborators.^{7, 8} It is curious that the experimental demonstration of this surprising relationship has aroused so little interest either among physiologists, pathologists or clinicians. There are hardly any references to it in the text-books. But there is a definite pathological condition, status lymphaticus, in which the most obvious abnormality is a persistent thymus, associated with hypoplastic lesions in the adrenal gland. In a summary of the clinical, pathological and experimental evidence Marine⁹ has shown that the condition produced experimentally is strikingly similar to that found as a disease in man, although the name given to the disease, "status lymphaticus" or "status thymolymphaticus," gives undue prominence to a symptom rather than to the underlying cause. But this is no reason why the existence of this syndrome, adrenocortical hypofunction with hyperplasia of the thymus, as a separate and definite clinical entity should be refused recognition, as has been done officially in England.

I pass on, now, to the changes in the adrenal medulla observed in animals subjected to prolonged estrinization. They are not nearly as striking as those seen in the cortex. The medulla exhibits a moderate

degree of active secretion, so that this part of the adrenal certainly does not show an inhibition. But the activity of the medulla is not sufficiently impressive to be in itself accepted as evidence of a secondary compensatory secretion of an antagonistic hormone similar to the process seen in the anterior pituitary. There is, however, other, indirect evidence to add support to such a conclusion. As already stated, adrenalectomized animals in which a small cortical adenoma has remained, react to estrinization at least as readily as intact animals. This seems surprising since the amount of cortical tissue present is often minute, less than a pin's head. But such animals do not contain any medullary cells. If the functional activity of the medulla can be assumed to counteract the estrogenic hormone, this high sensitivity to estrogenic hormones of animals completely devoid of medullary cells, but possessing a small amount of cortical tissue, can be accounted for. The study of the adrenal gland of various highly inbred strains of mice with a high and a low incidence of mammary cancer has brought to light facts which lend further support to this conclusion. There are inbred strains of mice which by their high incidence of spontaneous mammary cancer in females indicate a high susceptibility to mammary cancer and to the action of the estrogenic hormone. Thus, in the males of high cancer strains this hormone induces mammary cancer more rapidly and in much greater number than in the males of low cancer strains. Now in two such high cancer strains which have been examined, the adrenal medulla undergoes spontaneously a process of brown degeneration which begins at an early stage and is progressive, so that eventually it destroys the greater part of the medulla.⁴ It occurs in practically every animal, both male and female, of the two high cancer strains examined, and in the females it is already present before cancer develops spontaneously. In a considerable number of other strains which have a very low incidence or do not develop cancer at all, this process of brown degeneration either does not appear at all in the medulla or if it does develop, it does so late in life and is then very circumscribed in its extent.¹⁰ This spontaneous disease of the adrenal medulla, which diminishes the functional activity of the medulla, is thus associated with a high susceptibility to the effects of the estrogenic hormone and also with a greater susceptibility to the general effects of this hormone. The work of H. S. N. Greene¹¹ on inbred rabbits has disclosed a very similar condition—the spontaneous development of pathological changes in the adrenals

and in the pituitary in association with the spontaneous development of mammary cancer. This association—increased susceptibility to the ovarian hormone and diminished functional activity of the adrenal medulla—suggests again an antagonism between the ovarian and the medullary hormones. The two parts of the adrenal gland secrete therefore two hormones which in their relation to the ovarian estrogenic hormone oppose each other. It is interesting to note that the same conclusion of a functional antagonism between the two parts of the adrenal gland has been arrived at by Marine as the result of his studies on the thyroid gland and its relationship to the rest of the endocrine system.

The functional relationship of the ovarian estrogenic hormone to the anterior pituitary and the adrenal glands is therefore a complex one. Like the relationship between the thyroid, the adrenal medulla and the islets mentioned at the outset of this lecture, it arranges itself into a pattern of an endocrine balance between synergists and antagonists. The anterior pituitary and the adrenal medulla secrete hormones antagonistic to the estrogens, the adrenal cortex a synergistic one. A disturbance of this balance produced by the excessive functional activity of the ovarian hormone leads to a secondary compensatory inhibition of its synergist, the adrenal cortex, and a secondary compensatory stimulation of its antagonists—the anterior pituitary and the adrenal medulla. These responses tend to restore the balance. Huse, in a book with the piquant title, “The Illiteracy of the Literate,” criticizes loose argumentation based on abstract terms. He says “Unfamiliar terms are understood by translation into the familiar, abstractions by translation into concrete terms. We have no guide except our own experience.” I have therefore translated this abstract relationship of a balance into concrete terms. I have attempted to represent this by devising the following diagram which represents literally an endocrine balance. As this diagram, Figure 2, was drawn up originally with the special view of its bearing on cancer of the mamma, the movements of the pointer indicate the changes taking place in the mamma. But the mamma could be replaced by some other organ, such as the testis, or by some general condition of the organism, such as skeletal growth, or obesity and emaciation.

The endocrine organs concerned in this balance have been restricted to the anterior pituitary and the two parts of the adrenal, because the

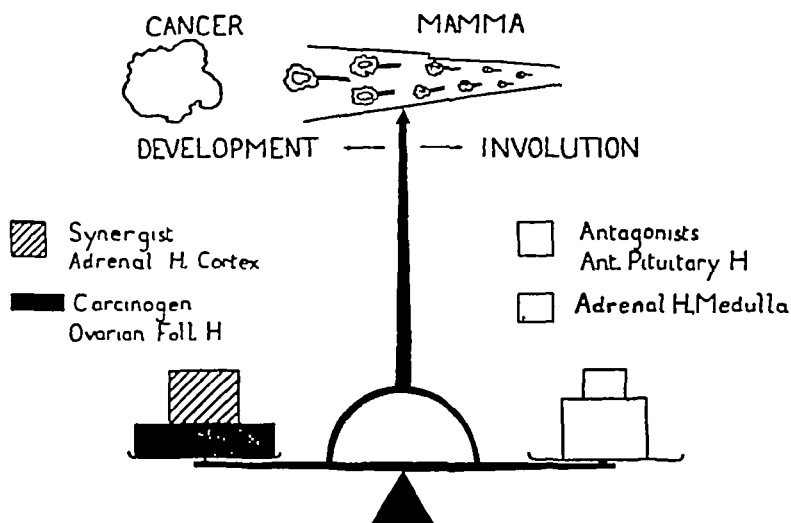


Fig 2—Diagrammatic representation of an endocrine balance

functional relationship between these three glands and the estrogenic hormone is almost certainly a direct one. The changes in the testis, the thyroid and parathyroids and the islets are probably secondary to those in the anterior pituitary, so that the anterior pituitary provides a relay mechanism by which the effects of one hormone may be transmitted to other endocrine glands. This diagrammatic representation affords an interpretation of the perplexing complexity of changes in the whole endocrine system which appear as the result of a prolonged excessive supply of the ovarian estrogenic hormone. It provides a working hypothesis the correctness of which can be tested by the results of experiments. The partial or complete inhibition of the effects of prolonged estrinization by adrenalectomy on the one hand, by a continued supply of an anterior pituitary hormone on the other, the partial functional replacement of the secretory activity of the ovary by the adrenal cortex, as revealed by the work of Little and his co-workers, the association of a spontaneous degenerative process in the adrenal medulla with an increased susceptibility to the estrogenic hormone, can all be read off from this diagram.

An excessive supply of the estrogenic hormone of the ovary depresses the left scale. In order to bring back the balance to its zero point the organism reacts to this excessive supply of the estrogenic hormone by an inhibition of the adrenal cortex, which secretes a synergistic hormone. Such an inhibition is represented by the brown de-

generation in the adrenal cortex. There is also a compensatory stimulation of the glands secreting the antagonistic hormones, the hyperemia and hypertrophy of the anterior pituitary with disappearance of the acidophile secretion and the slight stimulation of the adrenal medulla. The difference in the relative sizes of the weights representing these two glands in the diagram is intended to indicate differences in the degree of their relative antagonistic action as judged from their compensatory stimulation. Experimentally the endocrine balance can be restored either by a continued administration of an anterior pituitary hormone represented histochemically by the acidophile secretion, or by the removal of the adrenals. The synergistic effect of the adrenal cortex being stronger than the antagonistic effect of the medulla, the net result of a complete removal of the adrenal is a weakening of the synergistic cortical effect. A disturbance of the endocrine balance in the same direction as that induced by an excessive supply of the ovarian hormone can be induced by a diminution of the functional activity of its antagonists. This is represented by the spontaneous brown degeneration of the medulla in some inbred strains of mice with a high susceptibility to mammary cancer. In theory a primary disease of the anterior pituitary which specifically diminishes or inhibits the secretion of the acidophile cells should also be able to bring about a depression of the left scale with—amongst other things—an increased susceptibility to mammary cancer.

The opposite movement of the endocrine balance, an upward movement of the left scale, can be brought about by a removal either of the ovaries or of the adrenals. As just stated, adrenalectomy owing to the preponderance of the synergistic cortical effect has as a net result the removal of this synergistic cortical hormone. If the adrenals are removed there is an attempt by the organism to restore the balance by an inhibition of the antagonistic function of the anterior pituitary gland, which now does not respond as readily to the effects of the estrogenic hormone as in the intact animal. Experimentally the balance can be restored by an additional supply of the estrogenic hormone, and we have seen that this protects the organism against the loss of the adrenal cortex. The work of Woolley, Fekete and Little, on the effects of ovariectomy, which I have mentioned, also conforms to it. In their ovariectomized mice the endocrine balance was restored spontaneously by a nodular hypertrophy of the cortex in accordance with

the position of the adrenal cortex in the diagram. The point of general importance which emerges from these considerations is that a swing of the pointer to the left or to the right can be brought about in a variety of ways, or in terms of pathology, this means that a given syndrome may be due not to *one* particular change in *one* particular endocrine gland, but to *different* changes in several *different* endocrine glands.

As already stated, the significance of the changes in the thyroid, parathyroid and the islets requires further investigation. There is a marked enlargement of the islets and of the parathyroids, while the thyroid is small, pale and histologically presents a resting condition. It is possible that some of these changes are induced, not directly in response to the excessive supply of the estrogenic hormone, but, like the atrophy of the testis, indirectly as the result of the secondary changes induced in the pituitary. But it is clear that directly or indirectly the action of the estrogenic hormone embraces a wider range of endocrine activities than that of any other single hormone.

In this respect it stands in striking contrast to the male sex hormone, testosterone, in spite of the close chemical similarity of the two hormones. It is evident from their chemical similarity that both are formed from the same mother substance and it is probable that these two substances represent two stages in the same chemical process, the female hormone being probably the end product, while the male hormone represents an intermediate stage. This accounts for the otherwise remarkable fact that both these hormones are present in the male and in the female, and that, for instance, large amounts of the female sex hormone have been isolated from the testes of stallions. To those who are romantically inclined it may appear as a disappointment that the tragedies of star-kissed lovers, of Romeo and Juliet, of Abelard and Heloise, and of thousands of other mute inglorious ones were brought about by an additional CH_3 group and the absence of a double linkage. As Greta Garbo says in *Ninotchka*, love is simply a question of chemistry. Since both sex hormones are present in the male and in the female, what we call masculinity and femininity results not from the presence of one sex hormone and the absence of the other but from a different hormonal balance between the two.

The most important difference between the two is that the female sex hormone is much more powerful than the male one. An excessive

supply of the male sex hormone—even in large doses—does not produce any of the striking effects on the pituitary and on the adrenal cortex which can be induced by very small doses of the female hormone. The anterior pituitary is *not* enlarged or congested and there is *no* brown degeneration in the adrenal cortex after the prolonged administration of testosterone. There is, however, evidence that some functional relationship between the male sex hormone and the anterior pituitary and adrenal glands exists. This relationship manifests itself when the testes are removed. In the anterior pituitary some of the cells undergo a degenerative change which disappears again when testosterone is supplied experimentally. A striking change is produced by castration also in the adrenal medulla¹. The peripheral cells of the medulla lose their adrenalin content partly or completely, so that the functional part of the medulla i.e. the number of medullary cells containing adrenalin, is greatly diminished indicating an inhibition of the functional activity of the medulla. The medullary cells which have lost their adrenalin content lose thereby their characteristic morphological appearance as medullary cells especially when they are examined by the routine histological methods. They have thus been mistaken for cortical cells. There is also a change in the innermost zone of the cortex, the zona reticularis, the cells of which enlarge and assume a morphological appearance very similar to the peripheral cells of the medulla which have lost their load of adrenalin. The appearance is thus created of the formation of a new zone of the cortex. But this new zone is not an addition to the gland, for the gland shows no corresponding increase in size. This zone has been formed mainly at the expense of the medulla, which is diminished in size and which no longer shows a sharp separation from the cortex but has an irregular outline with islets of adrenalin containing cells lying within this new zone separated from the central medullary mass. The appearance of the adrenal gland of a male mouse after castration is thus similar to that seen in young female mice, but rarely in old females. The apparent new zone is, in fact, the so-called X zone about which so much has been written in the literature to the effect that it is an independent zone. This view is untenable both on mechanical and on experimental grounds⁴. It is due to the use of histological methods not adequate for investigations of this kind. When testosterone is administered to castrated male mice, the broad zone, i.e., the X zone, rapidly disappears again without any corresponding alteration in the

size of the gland. It disappears because the peripheral cells of the medulla, which had lost their load of adrenalin, become filled again with adrenalin granules and because the innermost cells of the cortex shrink. The result is that the central medullary mass of adrenalin-containing cells increases in volume and presents again a regular outline sharply differentiated from the cortex. The estrogenic hormone shows a significant difference from the male sex hormone in not being capable of producing this effect. The diminution in the volume of adrenalin-containing medullary cells when the male hormone is absent is clearly an inhibition, the increase in volume by replacing the missing testosterone is equally clearly a stimulation. This effect corresponds to the relationship given in the table shown at the beginning as existing between glands secreting antagonistic hormones. The swelling of the innermost cells of the cortex after castration indicates a stimulation, in agreement with the known function of the cortex of forming both male and female sex hormones. The cortex is thus a synergist to the endocrine functions of both the male and the female gonads. It reacts accordingly by increased functional activity when the gonads are removed, and by inhibition when the male or the female sex hormone is administered.

The adrenal changes following removal of the testes and their disappearance by the administration of testosterone are the most striking features in the relationship of the male sex hormone to the other endocrine glands which have been found so far in addition to the well-known castration effect on the pituitary. It may be recalled for purposes of comparison that the outstanding effect of the estrogenic hormone on the adrenal is also an inhibition of the cortex and a stimulation of the medulla. But with the ovarian hormone these effects manifest themselves differently, and are more pronounced in the cortex, while it has only a weak stimulating effect on the medulla. Perhaps that quality which we call "virility," as distinct from virilism, is a manifestation of the strong stimulating effect of the male sex hormone on the adrenal medulla. It is not fanciful to see a connection between the wide range of endocrine activities capable of being influenced directly or indirectly by the female sex hormone and that quality of femininity. "The infinite variety which time cannot wither nor custom stale." There is abundant evidence that the functional activity of some endocrine organs affects the mind and can, in turn, be affected by the mind. The shivering of fear of cold and of a high fever have the same origin in the secretory

activity of the adrenal medulla. The difference between the nervous, restless, excitable hyperthyroid and the slow, dull, apathetic hypothyroid is another example. This difference between the male and the female sex hormones may also be correlated with the greater frequency in women of psychoses in disturbances of ovarian function such as menstruation, the puerperium, lactation and the menopause.

The hormonal relationship between the ovary, the anterior pituitary and the two parts of the adrenal gland conform to the same general pattern which exists between the adrenal, the thyroid and the pancreatic islets and which we represented in Table I. It indicates that a functional activity of an endocrine gland can be elicited as a compensatory phenomenon either by the hyperfunction of its antagonist or by the hypofunction of its synergist.

This interrelationship affords an explanation of the position of the pituitary gland in the endocrine system. At present it is generally believed that this gland *dominates* the endocrine system. It has been described metaphorically as "the leader of the endocrine orchestra." This conception is, as far as I know, based mainly on the fact that removal of the pituitary is followed by atrophic or degenerative changes in almost all the other endocrine glands and that different extracts of the pituitary have the power to repair these degenerative changes. But we have seen that the excessive functional activity of another endocrine gland, the ovary, can produce a syndrome very similar to that following a hypofunction or removal of the pituitary. It is clear, therefore, that the pituitary is by no means the leader of the endocrine orchestra. The evidence presented shows that the pituitary is deeply influenced by the female member of the endocrine orchestra. The relationship between the ovary and the pituitary is, in fact, a reciprocal one, the two glands secreting hormones which antagonize each other. There is evidence of a similar reciprocal relationship between the pituitary and some other endocrine glands. The pituitary changes resulting from the activity of other endocrine glands have been studied in greatest detail in their relationship to the male and female gonads and to the thyroid gland. From the survey of Sevringhaus on the anterior pituitary, the three conditions, castration, pregnancy and thyroidectomy, produce the same pituitary changes, a hypertrophy of the gland with a diminution of the acidophile cells and an increase in the basophiles. The administration of the thyroid hormone to a thyroidectomized

animal restores the number of acidophiles From a study of the inter-relationship of the thyroid and the anterior pituitary Marine and his collaborators¹³ come to the conclusion that the anterior pituitary is as much under the influence of the thyroid hormone as the thyroid is influenced by the anterior pituitary hormone There is evidence that the anterior pituitary is also affected by the functional activity of the adrenal cortex If we speak of the pituitary hormones as gonadotropic, thyrotropic and adrenaltropic, we can equally well speak of the hormone of the gonads, thyroid and adrenals as pituitarytropic The term "tropic" as applied to the pituitary hormones is a vague one, and it is very properly vague It indicates merely the existence of an interrelationship, and should not be taken as predicating that this relationship is a direct and one-sided one As a working hypothesis the so-called "tropic" effect of anterior pituitary hormones on some other endocrine glands may be regarded as the manifestation of the functional relationship existing between endocrine glands secreting antagonists as shown in Table I

We thus get a glimpse of the position held by the anterior pituitary in the endocrine system, it is a compensatory mechanism which comes into play when the primary functional activity of another endocrine gland disturbs the endocrine balance That is its physiological response Pathological conditions result when the capacity of this compensatory mechanism is strained by the effect on the anterior pituitary of a prolonged, primary change in another endocrine gland The pituitary then undergoes more profound changes as a secondary effect By virtue of the relationship of the pituitary to the other endocrine glands, the altered pituitary acting as a kind of relay induces in them, as a tertiary effect, functional activity or functional inhibition, thus producing a multiglandular endocrine disturbance If this conception be correct, one would expect to find diseases of *one* endocrine gland, especially diseases which are slow to develop, to be associated with pathological changes in some other endocrine glands and especially in the anterior pituitary Furthermore, there is the possibility that the gland most obviously affected may not be the primary cause of the disease, even though it is at present generally regarded as such There is already a group of endocrine disorders of obscure origin and classed together as multiglandular diseases But, until recently, most endocrine diseases have been generally identified with a diseased condition of one single endocrine gland

Exophthalmic goiter is an example par excellence. It has been generally identified with hyperthyroidism. Hyperthyroidism is one feature of its syndrome. But it has been difficult to induce exophthalmos experimentally by giving thyroxin. Schockaert¹⁴ and Loeb and his co-workers¹⁵ have made the interesting discovery that exophthalmos can be induced experimentally in young animals by the injection of anterior pituitary extract. Subsequently Marine and his colleagues found that the experimental production of exophthalmos is facilitated by subtotal thyroidectomy, and furthermore that the exophthalmos thus produced can be made to disappear by the administration of thyroxin. As the result of his experimental and pathological observations Marine¹⁶ has arrived at the conclusion that the presence of exophthalmos in Graves' disease is dependent on two factors: thyroid insufficiency and pituitary hyperactivity. He suggests that the primary endocrine disturbance leading to the syndrome of Graves' disease lies outside the thyroid, probably in the testis or in the adrenal cortex, where pathological changes are frequently found in Graves' disease. This primary endocrine disturbance induces a hyperactivity of the thyroid as a compensatory response.

Another example is Cushing's syndrome which Cushing himself associated with a basophile adenoma of the pituitary. But the same syndrome has also been found in cases where the anterior pituitary was normal or only slightly abnormal, but where there was a hyperplasia of the adrenal cortex, or an arrhenoblastoma of the ovary and even in cases of malignant tumor of the thymus. This is a demonstration of the important fact, emphasized in another part of this lecture, that the same syndrome can be induced by different combinations of endocrine disturbances. Another example of this remarkable fact is supplied by the paradox mentioned at the outset of this lecture. The syndrome, produced experimentally by removal of the pituitary, or known clinically as Simmonds' disease, where it is associated with a degenerative disease of the anterior pituitary, has been produced by us experimentally by an excessive supply of an ovarian hormone. In the last mentioned condition, the syndrome is associated with an enlarged and deeply congested pituitary, which has been exhausted by prolonged functional activity and may present the condition of a chromophobe adenoma. This does not imply that the three conditions are identical, either etiologically or symptomatically. In Simmonds' disease, as after hypophy-

sectomy, the mamma is atrophic. The difference in the condition, induced by the estrogenic hormone, is the presence, even in males, of a well developed mamma or even of mammary cancer. The point I wish to make again is that a characteristic group of symptoms can be induced from different endocrine angles. It has been argued that the doses of estrogenic hormones necessary to induce pathological changes in the pituitary and the adrenals are so large, that they can have no bearing on the etiology of similar conditions in the human subject. But Bagg¹⁷ has succeeded in producing similar lesions in the pituitary and the adrenals by subjecting the ovaries of rats to the functional strain of rapidly repeated breeding. These observations of Bagg conform to the work of Greene¹¹ mentioned previously in showing that the ovary can under abnormal conditions secrete sufficient hormone to induce pathological changes in other endocrine organs.

The part played by the islets in the etiology of diabetes mellitus is, I believe, still obscure in the sense that pathological lesions of sufficient severity to account for the condition are not always present. Perhaps here, too, some other glandular lesion is involved. Obesity is still another example of a syndrome which can be reached from divers endocrine angles. The physiology of adipose tissue is a subject which has received little attention, as Gideon Wells points out in a recent review of the literature entitled "Adipose Tissue: A Neglected Subject."¹⁸ But both as a physiological and as a pathological problem it has hidden scientific charms. The formation of fat in the organism is dependent on a glandular structure, dispersed throughout the body in small cellular aggregations and subject to endocrine influences, as I pointed out 20 years ago. Pathological obesity can result from a primary dysfunction either of the gonads or of the anterior pituitary or of the thyroid, and, according to some authors, also of the pancreatic islets.

It is perhaps appropriate to mention in this connection that the possibility of inducing profound changes in the pituitary and the other endocrine organs as the result of the prolonged administration of estrogenic hormones should be borne in mind in the therapeutic administration of this ovarian hormone over prolonged periods. This is a danger which is more likely to be incurred than the more remote, although the more serious one, of inducing cancer of the mamma. Of this latter possibility I have already expressed my opinion in other papers. I need not refer to it again, therefore, beyond saying that the therapeutic

value of the estrogenic hormones is so high that their use should not be discredited by either overrating or underrating the dangers resulting from their use. In my opinion there is no danger in the therapeutic administration of an estrogenic preparation over short periods of time of several months, in doses just sufficient to produce the desired therapeutic effects. When this hormone has to be given over prolonged periods of a year or several years, the danger of inducing endocrine changes can be avoided by giving the estrogens in therapeutic doses and discontinuously in courses lasting for three or four months, interrupted by periods of rest. The administration of estrogenic hormones by the inoculation of pellets is, I believe, dangerous and inadvisable.

SUMMARY

I have tried to lay before you a conception of the endocrine glands as forming a single system of great complexity and delicacy, in which the functional activity of each individual gland is regulated partly by that of its antagonists and its synergists. It thus enables a highly differentiated organism to adapt itself effectively to changes in the external and internal environment. The test of such physiological conception is its applicability to diseases of the endocrines. As our knowledge of the pathology of these conditions advances it is becoming increasingly evident that in many of them more than one endocrine organ is involved and that their etiology is much more complex than simply the identification of such a disease with a pathological condition in one single gland. An ideal pathological examination of a case of an endocrine disease should, therefore, involve the examination of every endocrine organ. Such material if collected in an endocrine register would materially advance our knowledge of the etiology of endocrine diseases by making it possible to correlate these conditions with experimental observations. And I may add that there are still a number of conditions not yet recognized as of endocrine origin, in which profound changes can be seen in such organs as the thyroid or the adrenal. I speak from personal experience when many years ago I collected material from autopsies of cases which had died in hyperpyrexia, the microbic origin of which had not been established.

From a confused heap of pieces of a picture puzzle we have taken some and tried to put them together without any preconceived notions. The picture which I have described to you has resulted. It is an attempt

at a functional integration of a group of endocrine organs

All I claim for the views I have expressed tonight is that they are a working hypothesis based on experimental observations. A working hypothesis is one which stimulates work with the object of either confirming it, or of refuting it by replacing it by a better one. If I have attained this object I shall feel that I have fulfilled the obligation which I undertook when I accepted the invitation with which you have honored me.

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THE BLOOD PLASMA FOR GREAT BRITAIN PROJECT*

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It seems appropriate to report to this Committee on the present status of the Blood Plasma for Great Britain Project for which the Academy is indirectly responsible, as it was initiated by one of the Academy's many protégés the Blood Transfusion Betterment Association. The development of this project is an example of how the Academy, largely through its Committee on Public Health Relations, has not only a local and national, but even an international influence in the field of public health.

Because we had been informed from reliable, authoritative sources that the Allies, particularly the British, were in urgent need of appropriate blood substitutes for the emergency treatment of shock and hemorrhage, on June 12, 1940, a special joint meeting of the Board of Trustees and the Board of Medical Control of the Blood Transfusion Betterment Association was called at the Academy to discuss the question of supplying the Allies with blood plasma, which does not require blood grouping, as the most effective product for their needs. To this meeting were invited Herbert B. Wilcox, the Director of the Academy, Alexis Carrel and several other scientists who have been working especially on blood preservation and blood substitutes, Captain Douglas B. Kendrick, Jr., Medical Corps, representing the Surgeon General of the Army, and representatives of the various larger commercial houses who are preparing and marketing blood serum or plasma. It was decided that we should act at once and this meeting was immediately followed by a meeting of the Board of Trustees where it was voted that the Association sponsor the production and shipment of blood plasma to the Allies provided the American Red Cross was willing to cooperate. The Board of Trustees voted an appropriation of \$15,000 from their treasury toward financing this project. At a subsequent meet-

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ing on August 1, an additional appropriation of \$5,000 was voted, to be reserved for research

On June 18, Mr John F Bush, President of the Board of Trustees of the Blood Transfusion Betterment Association, Mr Tracy S Voorhees, a member of the Board, and I went to Washington and had a lengthy interview with Mr Norman H Davis, Chairman of the American Red Cross, his chief aide, Mr DeWitt C Smith, Director of Domestic Operations, and William DeKleine, Medical Adviser We presented our tentative plan for the organization of the blood plasma project They were much interested and very sympathetic, especially in view of the fact that we pointed out to them that, in addition to this work for the Allies who, of course, since that time have come to mean the British, the development of this project would eventually be of great use for our own national defense program in supplying plasma to our armed services They, however, at that meeting were rather noncommittal as to what assistance they would give us

Later the same day we had an interview with Colonel Charles C Hillman, Medical Corps, of the Office of the Surgeon General of the Army, who was very encouraging and who referred us to the special Subcommittee on Blood Substitutes of the National Research Council, of which Cyrus C Sturgis, Professor of Medicine of the Medical Department of the University of Michigan, is Chairman The Army was being guided on this question by the advice of this Subcommittee Contact was promptly established with Sturgis who endorsed our plan wholeheartedly After considerable correspondence and telephonic conversations to and fro, on July 26, Mr Bush, Mr Voorhees and John Scudder, whose enthusiasm for the project was a great stimulus to us and who was subsequently appointed Assistant to our Board of Medical Control, again had a conference in Washington with Mr Norman H Davis, Mr Ernest J Swift, one of the Vice-Chairmen, and Mr DeWitt C Smith The result of this conference was that the Red Cross agreed to cooperate with us to the extent of advancing us \$25,000, with an eventual additional grant of \$5,000, and of conducting the publicity campaign to obtain for us the necessary volunteer donors The Blood Transfusion Betterment Association was to direct the procuring of blood and the production of the plasma The plasma was then to be delivered to the Red Cross in New York City which would attend to its shipment abroad

We commenced immediately with six hospitals: Presbyterian, Mount Sinai, New York Post-Graduate, New York, Long Island College and Memorial, and in the beginning of October two other hospitals, Lenox Hill and Hospital for Joint Diseases, were added. Four additional hospitals have now been approved by the Board of Medical Control and will function if required: French, Ruptured and Crippled, Brooklyn Hospital and Jewish Hospital, Brooklyn. Most of these hospitals have installed the major equipment needed, such as iceboxes, incubators, centrifuges and electric pumps. In exceptional instances we have furnished a centrifuge or a centrifuge head and cups. In all cases we have supplied transfusion sets, bottles, stoppers, caps, labels, record books, record cards and release forms. Of course, the service of all the doctors, nurses and technicians is donated. We pay the hospital \$1.50 per liter of the finished product for out-of-pocket laboratory expenses, etc.

The Academy, which has always been most generous in giving us meeting rooms, presented us with commodious quarters for a central managing, recording and donor distributing office and an elaborate telephone and record system was at once established in these quarters. Mr. Morris M. Davidson volunteered his services and was appointed Director of what we have called the Blood Plasma Division of the Association. A staff of twenty-two paid secretaries, clerks and telephone operators was eventually employed. Pettit & Reed offered us the services of a special refrigeration truck for collection of the product from the various hospitals and the facilities of their refrigeration warehouse for storage until shipment by the Red Cross. The call for volunteer donors by the Red Cross was made through the press, over the radio and by the wide distribution of descriptive posters and pamphlets. It apparently had a very strong popular appeal, judging by the immediate enthusiastic response from every stratum of society. The first appointments for donors were made at The Presbyterian Hospital on August 15. Twenty-two donors were sent and twenty were accepted. The following day six donors were handled by The Mount Sinai Hospital. Since that time there has been an ever-increasing stream and, up to and including October 31, 9,556 appointments have been made—1,044 in August, 3,822 in September and 4,690 in October (Table I).

The actual number sent to hospitals was 8,132. Of these 1,171 did not appear, 6,961 actually arrived at the hospitals. To this number 404 were added by the hospitals themselves. Of this total of 7,365, 381, or

TABLE I

ANALYSIS OF APPOINTMENTS FOR DONORS BY HOSPITAL AND MONTH

Hospital	August	September	October	Totals
Presbyterian	762	1203	1012	2977
Mount Sinai	199	577	901	1677
New York Post-Graduate	12	555	791	1358
New York	11	469	552	1032
Long Island College	60	464	422	946
Memorial		391	363	754
Lenox Hill		134	264	398
Joint Diseases		29	385	414
Totals	1014	3822	1690	9556

TABLE II

ANALYSIS OF DONORS BY HOSPITAL AND EVENT

Hospital	Donors Sent	Donors Lapsed	Donors Arrived	Donors Added by Hospital	Donors Rejected	Donors' Bloods Taken	Donors' Bloods Discarded
Presbyterian	2025	371	2254	132	120	2266	31
Mount Sinai	1415	203	1212	75	28	1259	5
New York Post-Graduate	1093	177	916	73	49	940	6
New York	956	102	854	14	56	812	12
Long Island College	759	144	615	60	28	647	14
Memorial	591	75	516	30	44	502	2
Lenox Hill	311	58	253	9	19	243	8
Joint Diseases	382	41	341	11	37	515	2
Totals	8132	1171	6961	404	381	6984	75

5.17 per cent, were rejected because of under- or over-age, general physical ineligibility, poor veins, low blood pressure, low hemoglobin percentage, history of communicable diseases, and acute upper respiratory infection or other pathology. The blood was actually taken from the remaining 6,984 donors. The blood from 75 donors, or 1.07 per

TABLE III

ANALYSIS OF WEEKLY QUOTAS OF DONORS FOR EACH HOSPITAL

Hospital	Donors
Presbyterian	250
Mount Sinai	240
New York Post Graduate	180
New York	150
Long Island College	100
Memorial	85
Lenox Hill	72
Joint Diseases	100
Total	1177

TABLE IV

ANALYSIS OF PLASMA SALINE SOLUTION RELEASES
BY HOSPITAL, MONTH AND QUANTITY

Hospital	Liters				
	August	September	October	November 1	Totals
Presbyterian	21	156	222		399
Mount Sinai		24	162	54	240
New York Post-Graduate			18	36	54
New York			12	60	102
Long Island College			90	23	113
Memorial			12		42
Totals	21	180	576	173	950

cent, was discarded because of positive or suspicious serology. The statistics from the various hospitals through October 31 are shown in Table II.

The eight cooperating hospitals are now prepared to handle 1,177 donors each week. The weekly quotas are shown in Table III.

The four additional hospitals, previously referred to, are each prepared to take 75 donors weekly, or an additional total of 300.

TABLE V

ANALYSIS BY HOSPITAL AND QUANTITY OF PLASMA SALINE
SOLUTION AWAITING RELEASE IN WAREHOUSE

Hospital	Liters
Presbyterian	156
Mount Sinai	168
New York Post-Graduate	174
New York	90
Long Island College	102
Memorial	66
Lenox Hill	24
Joint Diseases	30
Total	810

Up to and including November 1, 1940, 950 liters of plasma saline solution have been released to the Red Cross as sterile and ready for shipment from the six hospitals originally cooperating (Table IV)

The latest report that we have on November 1, is that 747 liters of this solution have already been shipped abroad. In addition to this amount released for shipment through November 1, there were 810 liters of the solution at Pettit & Reed's waiting for the very rigid two weeks' culture quarantine that we have instituted and that is being controlled by our Bacteriological Consultant, Frank L. Meleney of The Presbyterian Hospital, who has very graciously placed his laboratory at our disposal for this purpose. This material comes from the eight cooperating hospitals as shown in Table V.

Further, there were about 700 liters of pooled plasma, equivalent to 1,400 liters of the final product, distributed in the iceboxes of the eight cooperating hospitals awaiting local culture reports before being added to the saline solution and sent to the central warehouse. Up to date, there have been 30 liters, or 3.15 per cent, of the solution lost because of contamination as checked by our central laboratory. This contamination was mostly in the early batches. Only one carton of 6 liters has been discarded in the last three weeks of October. Four

hospitals have reported losses due to contamination found in the hospital—the total amount of these losses being approximately 20 liters of plasma or what would have made 40 liters of the solution.

As yet we have had no reports from London as to the real results from the use of the plasma but we have had a letter, under date of August 27, from Sir Edward Mellanby, Secretary of the Medical Research Council of Great Britain, telling us that the first batch shipped had arrived in good condition, had been cultured, found to be sterile and would be placed at the disposal of the Royal Air Force. We have also had a letter, dated October 8, from A. N. Drury, Chairman of the Committee on Traumatic Shock and Blood Transfusion of the Medical Research Council of Great Britain, stating that 7 cartons, or 42 liters, of the plasma saline solution had arrived safely and was proving very useful. We further received a second letter from Sir Edward Mellanby, dated October 25, urging us to continue sending the plasma at least until the end of January, 1941, and stating that he felt that by the time this shipment arrived in the latter part of February, the production of plasma in Great Britain would be on a sound basis and sufficient to take care of their needs.

On October 3, Mr. Bush, Mr. Voorhees and I again went to Washington to report to Mr. Davis and his advisers. They seemed quite pleased with what we had accomplished and, though they gave us no definite promise, indicated that we could count on continued financial support, for even if Great Britain had no further need for our product—which question was to be investigated—they felt that we had the organization for developing the best method of mass production and for settling most of the doubtful points about blood substitutes.

When we began this work we were led to believe that it would be relatively simple. We received the impression that preparing plasma would not be much more difficult than mixing a cocktail, but we soon learned, much to our distress, that such was not the case. When we began mass production of plasma for shipment abroad, to be used after a relatively long period had elapsed, we found that it was a vastly different proposition than the production of small quantities of plasma in a hospital for prompt use on the premises.

Unexpectedly, innumerable problems came up—some of which we have solved, but not all, as yet. Let me enumerate some of the more important of them.

First of all, which is the better blood substitute and which gives the least reaction—plasma or serum? For the time being we have decided on plasma

Should we produce liquid or dried plasma? We settled on liquid plasma for the present as the equipment now in use for drying plasma was expensive, not entirely satisfactory and would take too long to install—and the time element was vital

Should the blood be collected by an open or closed method? We have settled on the closed procedure

How should the closed procedure be instituted? What type of bottle should be used—dumbbell, square straight-sided, or cylindrical? Should the neck be narrow or wide, straight or with sloping shoulders? What is the best size for the bottle? Should a double-holed, glass-tubed rubber cork or some form of vaccine stopper with a special double needle be used? Should vacuum, suction, or just the venous pressure be utilized in drawing the blood? If suction, what type? How should the blood be mixed with the sodium citrate solution? How should these bottles be corked or capped after filling? What is the best way of drawing off the supernatant plasma into the pool bottles? These questions are all being investigated at the moment. Some have been more or less settled, while some are still sub judice

What should be the age limits, the minimum blood pressure, and the minimum hemoglobin percentage for the volunteer donors? Over 21 and under 60 years, 110 systolic, and 80 per cent, respectively, were our answers

Should the blood be taken only from fasting donors to avoid turbidity of the plasma from fat globules? This was especially important in view of the fact that the British Medical Research Council had given instructions to their medical officers to discard turbid serum or plasma as turbidity probably indicated contamination. We preferred not to have the donors fast as they might faint more easily at the blood letting and as it was difficult from an administrative standpoint to get volunteer donors to abstain from eating. After explaining the situation by cable to the heads of the British Medical Research Council, they wired back that they would waive their objections in this respect for our product

Should Negro blood be utilized? This was answered in the affirmative but with the proviso that the plasma therefrom should be specially labelled as to its origin

What serological test for syphilis should be used? Any recognized test was considered acceptable

Should blood with a plus-minus luetic test be used? It was agreed that blood with even the slightest suspicion of a positive serology should be discarded

Should the blood of the donors be grouped? Although blood grouping is not necessary as regards the pooled plasma, it was felt that, nevertheless, the donors blood should be grouped for the donors' information as a slight reward for their donation. The Red Cross now furnishes every donor with a card stating that he or she has given his blood for this plasma project and on the card appears a notation of the donor's blood group

Is sedimentation or centrifugation the better method of separating the plasma from the blood cells, from the standpoints of yield, sterility, speed and economy? Both methods are now being used in the different hospitals and the question is being carefully studied, but as yet no definite decision has been reached

How much and what strength sodium citrate solution should be used? We have settled on 50 cc of a 5 per cent solution for every 500 cc of blood

What strength merthiolate solution should be used as a bacteriostatic and bactericide? We are now using 1 to 10,000, but there is some question as to its efficacy and an increase of strength is under consideration

What is the best type and size of pool bottle? We selected a two-liter Baxter bottle

How much normal saline solution should be added to the plasma to keep it from becoming too viscous and to prevent the precipitation of the fibrinogen? A 50 per cent dilution was agreed upon

Should the pH of the plasma saline solution be determined? This was felt to be unnecessary

What system should be used for transferring the plasma from the pool bottles to the final bottles so as to expose the product to the least danger of contamination, and what type and size of this bottle is the best for the packing and shipment of the solution? The Baxter vacuum system was thought to be the safest and we decided on a one liter Baxter Plasma-Vac bottle as the most advantageous

At what temperature should the pooled plasma and the plasma saline solution be kept until shipment abroad? Three to 5 degrees centigrade was our decision

How should the final bottles be labelled, what kind of record card should be kept at the hospitals, and how should the release signed by the donor be worded? These questions were easily answered

What size carton should be adopted for shipment? It could not be too large because much of the plasma was to be shipped by clipper, and one holding 6 one liter bottles was chosen as the most practicable

Finally, came the all-important question of bacteriological and toxicity control. This was the most serious problem but it is gradually being settled to our satisfaction. Careful bacteriological cultures of the pooled plasma are first made at the various hospitals—both aerobic and anaerobic—before the addition of the merthiolate solution. If these cultures from the pools are sterile after one week, the merthiolated plasma is added to the saline solution in the final bottles and sent to the warehouse. Simultaneously, a sample from each 2-liter pool in a 300 cc Baxter Transfuso-Vac pilot bottle is also sent to Meleney's laboratory and from this sample, cultures are made on the third, seventh and fourteenth day and animal tests for toxicity are likewise made. If the culture is sterile and the product is shown to be non-toxic, the bottles of solution from which the sample has been taken are released to the Red Cross for shipment abroad. This technique has worked out quite well but we are still not completely satisfied, and are about to investigate the question as to whether we would not obtain better results by filtering the plasma after converting it into serum by precipitating out the fibrinogen with a calcium salt. This conversion into serum is recommended as plasma apparently can only be filtered with difficulty and serum produced in this manner is thought by many to be safer than serum obtained from the simple clotting of blood. William Thalhimer has very kindly offered his services and the facilities of the Manhattan Convalescent Serum Laboratory to help us study this phase of the problem.

After innumerable meetings and conferences to settle these various questions, toward the latter part of September, the mounting difficulties which we encountered forced us to take a radical step and on October 1, we engaged a full-time, salaried Medical Supervisor to help us solve the technical problems, to formulate a standard, uniform technique and to coordinate the cooperating hospitals. The unanimous choice of the Board of Medical Control fell on Charles R. Drew, formerly of The Presbyterian Hospital and now Assistant Professor of Surgery of the Medical School of Howard University. The School was kind enough

to release him to us for a four months' period. Since Drew, who is a recognized authority on the subject of blood preservation and blood substitutes, and, at the same time, an excellent organizer, has been in charge, our major troubles have vanished. Drew is directly responsible to the Blood Plasma Committee of our Board of Medical Control. This Committee consists of Cornelius P. Rhoads, Chairman, Lester J. Unger and David C. Bull.

We also met some legal snags which the experts in the Department of Health have helped us to unravel.

What was to be done about positive serological tests for syphilis in the blood of these volunteer donors? Should the Department of Health be notified and should the donor be informed? There was no argument about notifying the Department. Section 105, Regulation 14 of the Sanitary Code of the City of New York makes this notification mandatory, but the Department agreed to treat the information discreetly through the agency of Theodore Rosenthal. Informing the donor was considered advisable and the method was left to the discretion of the respective hospital.

Must a complete physical examination including the genitals be made on every donor? This was of great importance as considerably over 50 per cent of the donors were women, many socially prominent and some unmarried. The Department ruled that Section 108, Regulation 5 of the Sanitary Code could be waived in the matter of genital examinations.

Must the Blood Transfusion Betterment Association or the cooperating hospitals obtain a license from the Federal Security Administrator to comply with Section 120, Paragraph 1 of Article 8 of the Sanitary Code? Walter T. Harrison, Chief of the Division of Biologics Control of the National Institute of Health of the U. S. Public Health Service, representing the Federal Security Administrator, ruled for us that he cannot license us or the hospitals as we are not engaging in this project commercially and the Board of Health, which has been most cooperative in every respect, is still taking the matter under advisement. A solution, I am sure, will soon be found.*

Several special research projects in connection with this work have been instituted to be financed through the amount set aside for research, as follows:

* The Board of Health at its meeting on November 12, 1940 after hearing the report of a subcommittee appointed to study the project, ruled that inasmuch as it was still in an experimental stage, and as the supervision now in effect appeared to be adequate no special regulations are called for at this time.

Lester J Unger has been given a grant to develop an appropriate double needle for withdrawing blood by the closed method and eventually for drawing off the plasma from the original bottle and transferring it to the pool bottle through the same needle

John Scudder has been given a grant to study the question of centrifugation vs sedimentation and also to develop an improved dumbbell bottle for collecting the blood

Cornelius P Rhoads has developed at the Memorial Hospital an improved apparatus for drying plasma or serum and will probably be given a grant for continuing this study * It appears that the development of a thoroughly satisfactory method of drying plasma or serum will be the eventual solution of the problem, because of the much greater stability of the dried product, its somewhat smaller bulk, the relative simplicity of packing, storing and transporting it, and the much lesser danger of loss from breakage We feel that Rhoads' apparatus may be superior to any now in use and our Association is very anxious to assist him in his research in this field

In addition, the Association also intends, eventually, to encourage and help finance studies, from every angle, on the respective merits of plasma and serum—either liquid or dry—as compared with fresh whole unmodified or citrated blood, and stored blood We believe that our group has the talent and the facilities, and with the financial aid of the Red Cross and the unlimited supply of volunteer donors furnished by this organization, we should soon be able to settle the major problems in regard to blood substitutes, the best method of their preparation and mass production, and their comparative values **

In conclusion, may I say that were it not for the broad-visioned sponsorship, and moral and practical support of the Academy, the Blood Transfusion Betterment Association would never have come into being and this constructive project, under its aegis, of giving vital assistance to the one remaining major democracy in Europe, of developing a direct and essential aid for our own national defense, and of eventually helping to solve all the moot points in the entire problem of blood substitution would have been impossible

* This grant was awarded to Rhoads at the meeting of the Board of Trustees, November 8, 1940
** The study of one phase of this problem namely a comparison from the chemical biological and clinical standpoints of plasma serum from blood and serum from plasma—both liquid and dried—was begun by Rhoads, Thallumer Scudder and others under the auspices of our Association on November 25 1940

GONORRHEA IN THE MALE*

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Assistant Professor of Urology University of Pennsylvania

PERHAPS as far back as medical history goes there has dwelt in the minds of those who cared for the afflicted a decidedly high state of confusion regarding what was the most appropriate treatment for gonorrhea. This confused state has reflected itself in an enormous percentage of the writings upon the subject, to the further bewilderment of those who read. It has, in the past, resulted in the carrying out of a large assortment of treatment methods that were highly inefficient and often caused far more trouble for the patient and his contacts than it was hoped they would relieve. One would be compelled to search far in medicine for any less soundly based therapeutic measures than those that so commonly were employed to cure this disease. It was only necessary for someone to laud a plan of treatment that was just a little easier to carry out, for him to get a multitude of followers. Often it seemed that the more bizarre and lacking in good judgment the plan might be, the more there were who adopted it.

It is not necessary that one be a keen student of this disease for him to discover just why these things were and, to an unfortunate extent, still are. He has but to enquire into the general lack of knowledge regarding the clinical behavior of gonorrhea under varying conditions to see why we have been in such a gullible state that we could be fooled so often. Having revealed this unfortunate fault of the past and wondered why men posted themselves upon these things in all other diseases before they started to treat them, an inquirer naturally would try to determine the present state of things in this regard. And, with all our scientific advances, he would find, to his surprise, that attitudes have not greatly changed. He would discover that the one great cry is, "How should we treat gonorrhea?" He would find reason to be disappointed if he asked many questions about the disease itself. Probably he would cry out himself, "Let's stop this mad rush long

* Presented October 18, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

enough to learn sufficient about gonorrhea to prevent our being perpetually fooled by one writer's dreams and another's faulty clinical interpretations" And, if his cries arrested the attention of us all to the end that we heeded, we would not travel up so many blind alleys or let others make us feel so ridiculous when "the tumult and the shouting dies"

Those who really know gonorrhea are seldom fooled. It is only those whose minds think only of treatment. And, if anyone is of the opinion that the age of gullibility has passed, he has only to look sensibly at what was and is done and said about sulfanilamide for the treatment of gonorrhea to realize that we have not all become so wise as we think. We were told by those whom we thought we could trust that this drug would cure anywhere from 60 to 91 per cent of all ambulatory males who had the disease. Thousands of us read these pronouncements and believed. We analyzed the case tabulations that so often were given and all but a very few failed to discover the "fly in the ointment." And there the fly stood, like Gargantua, grinning at us. It was in the first group of cases that "made" the newspapers and the magazines. And it stood out like the proverbial sore thumb in about every article that cited case reports.

It would not be so tragic if we were the only ones deceived. But the tragedy of the thousands upon thousands of women who have been infected because we did not see what was wrong should be hard for us to forget. Contemplation of this should stir the most somnolent of us into a feverish struggle to learn so much about gonorrhea itself that we never again could be led so widely astray. This is the greatest need of the day so far as this disease is concerned.

Just what was the "fly" in the chemotherapeutic "ointment?" The "fly" was simply this. If sulfanilamide cures gonorrhea, it does it well within the first two weeks of medication and if the patient has a gonococcus after that and eventually gets well—or seems to—he does so for the same reasons that he did before we had sulfanilamide, viz, time and other treatment. Nothing could be more erroneous than to attribute his cure to sulfanilamide. And, yet, we did just that.

What is the real truth about sulfanilamide so far as its effect upon gonorrhea is concerned? This drug does one of three things: (1) It either produces a cure well within two weeks, (2) it eradicates the obvious signs of the disease and leaves the patient as an asymptomatic

gonococcus carrier or (3) it does not in any way change the course of his disease

The first question that arises in the mind is How many does it cure? And the answer is that one has to be generous to a scientific fault to place the figure it is high is 30 per cent, which is a far cry from those romantic figures of from 60 to 91 per cent

The second question is How many asymptomatic carriers does it make? To this there is no exact answer but one would be guilty of no exaggeration if he placed his low figure at 20 per cent He might be more correct scientifically if he placed it much higher

We can dismiss the definite and obvious sulfanilamide failures by saying that they may be cured by some of our later sulfonamides and those who are not should be treated as cases were treated before these drugs came into use In other words we have not reached a point where the best of our former methods of treatment are in any sense outmoded, nor is it probable that we shall for some time to come, if we ever do

We and Society have little further vital interest in the prompt drug cures and we are not fooled by the obvious sulfonamide failures But both should be deeply concerned about those who become asymptomatic gonococcus carriers For a virile male who falsely believes himself cured is a social menace of no small proportions He brings into the clinical picture a number of things that formerly occupied but a small portion of it He may go months without any symptoms whatever, despite alcohol and sexual intercourse which, in the presulfonamide days, seldom left him in doubt about the question of cure When he transmits his infection to a female, she usually, if not always, becomes a totally asymptomatic carrier who has not the slightest suspicion that she has such an infection until she transmits it to a third party This unfortunate third party is never left in doubt He has an active infection characterized by a decidedly profuse urethral discharge containing countless gonococci Interestingly enough, this third party usually registers a prompt clinical response to sulfanilamide medication That he is not always removed from the seeming endless chain of infection is shown by the fact that he has an equal chance with the "party of the first part" of becoming an asymptomatic carrier

Thus could the sulfanilamide shaking-down process be continued, if time and space would permit, but it only would bring us to the point reached by the essayist and many of his friends, viz, sulfanilamide is

the poorest of the sulfonamides to use in the treatment of gonorrhea. It should be abandoned for the far more efficient ones, sulfapyridine and sulfathiazole or whatever the future may develop that may be improvements upon them.

As we turn to these better sulfonamides we should do well to avoid the impression that all is "moonlight and roses" and that we can forget the sad lessons of the romance of sulfanilamide. For they, too, produce some asymptomatic gonococcus carriers who can produce others of the same stripe. And there are beginning to return to our dispensaries patients whom we were sure were cured by both drugs some months before—patients who either without exposure, or too often after exposure for the usual incubation period, have developed an urethral discharge containing gonococci. Not only had these patients been subjected to all of our so-called tests of cure but their secretions repeatedly had been subjected to the most careful microscopic and cultural studies.

So far our story has been a decidedly disquieting and gloomy one and it is time to get out into the sunshine, for there is much of it. There are reports by a number of careful clinicians to the effect that the *apparent cure* rate of both sulfapyridine and sulfathiazole runs somewhere between 80 and 91 per cent. And there is little, so far, to suggest that the carrier rate among these *apparently cured* patients is a shockingly high one. Certainly it does not compare with that of sulfanilamide. Even if it eventually proves to be as high as 10 per cent, he who thinks in terms of public health must view the introduction of these drugs into the treatment of gonorrhea as the most glorious thing that has ever happened for its victims. Anything that well within two weeks cures 70 per cent or more of these patients has human values far beyond our powers of expression. None of us ever dreamed that such things would come to pass and, yet, they are here.

So much for the glory and the gloom of it all. Let us draw this to a close with a recital in terse statements of what our clinical experiences have taught us:

1. As blood concentration of these drugs is of no importance, except perhaps in metastatic gonorrhea, large doses are not needed.

2. If the patient is not symptom free by the end of five days, further administration of the same sulfonamide is useless.

3. Change to another may produce results. This is particularly so where sulfanilamide has failed, but reversal to sulfanilamide where the

others have failed is useless

4 If cure is to be obtained, it takes place probably in the first week

5 Continuation of the same drug for longer than ten days is of no value

6 The cure rates of sulfapyridine and sulfathiazole are about the same for both early and late cases

7 Thus we can abandon the idea, formerly held by some about sulfanilamide, that results were better in patients who had mustered up some immunity response. The drugs should be started at once

8 The toxic by-effects of sulfapyridine are, dose for dose, about equal to those of sulfanilamide. For sulfathiazole they are far less

9 As many of these toxic symptoms appear after the first week of medication some workers discontinue the drugs at the end of seven days. Their cure rates are not lower than those who continue for ten days or more

10 With any sulfonamide the patient should be seen by the physician every 48 or 72 hours

11 In the presence of any toxic symptoms of moment, these drugs should be stopped and the patient instructed to drink large quantities of water to aid in their elimination

12 Short dosage period and a fluid intake of at least 1500 cc in the 24 hours will prevent sulfonamide urinary calculosis

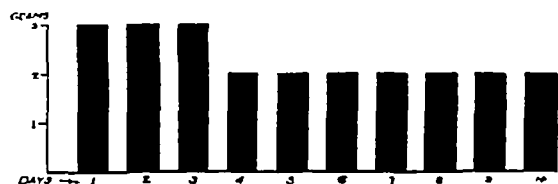
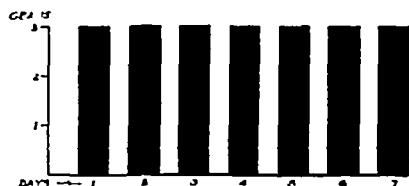
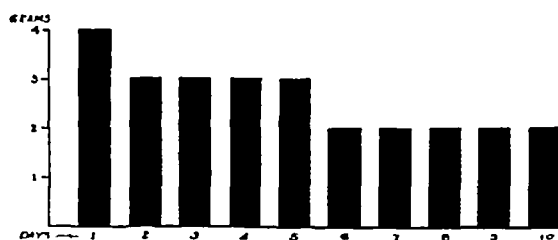
13 Patients seemingly cured have no urethral discharge for study, and in tests of cure the washed urinary sediment which contains urethral, prostatic and Cowper's gland secretions offers the only means of revealing carrier states microscopically

14 Properly done cultures of carefully collected secretions have twice the diagnostic value of the most carefully done microscopic studies and many times the value of haphazard microscopic methods. Both can fail to reveal persisting infection and should be repeated two or more times

15 Our older tests of cure, alcohol, sexual excitement and sounds usually fail to stir carrier states into clinical activity in sulfonamide cases

16 It is felt by some careful clinicians that post-sulfapyridine carrier-states do not lie dormant as long as those produced by either of the other drugs

17 It is the fixed opinion of most of those who have done most



Schemes of Sulfonamide Dosage Used by Some Careful Investigators with Approximately Similar Results

with cultures as tests of cure that no patient should be dismissed from observation in less than two months during which at least three cultural studies have been made

18 The lack of the general availability of cultural studies, together with the possibility of infection being missed by even the most careful, should make one hesitate about any highly enthusiastic pronouncements of cure

19 Under even the best of circumstances it is best to insist that the patient employ rubber sheaths in his sexual pursuits for three months after supposed cure. Most will not do so, but such an admonition relieves the physician of an unpleasant responsibility

20 At least 90 per cent of all urethral discharges are non-gonorrheal and a microscopic diagnosis of gonorrhea should be made before any patient is started on sulfonamide drugs. They are practically useless in non-specific cases

In the accompanying chart are outlined several schemes of dosage that apply to each of the sulfonamides and which have given the various workers about equal results

CURRENT TRENDS IN DIAGNOSIS OF
RENAL TUBERCULOSIS*

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DIAGNOSTIC or therapeutic procedures in medicine can never become completely standardized. As the various diseases are understood better, however, some standardization may be accomplished if broad basic principles in diagnosis and treatment can be established and accepted. This would be of distinct value to the medical profession, especially in the teaching of the subject to the medical student. Nowhere would some form of standardization in diagnosis be more welcome than in the subject of renal tuberculosis. The average medical student on graduation has no distinct picture of this disease. One instructor may warn his students against ureteral catheterization to obtain specimens of urine for examination for fear of infecting a normal kidney. Another may advise bilateral retrograde pyelograms in every case of suspected renal tuberculosis. Just what constitutes the indication for nephrectomy in this disease is likewise likely to be very confusing to the young physician. Not at all helpful in the clarification of this subject is the fact that within the last few years diagnosis has been altered radically by the introduction of excretory urography.

Renal tuberculosis has been a recognized disease for a sufficient time and excretory urography has now been used for a sufficient number of years so that it should be possible to evaluate methods of diagnosis somewhat. It may be that if our cases are carefully studied, the trend of diagnosis will be found to be undergoing considerable change. If so, opinions and teaching of this subject may require modification. A correlation of the views of the various schools of thought regarding this disease would be distinctly helpful. Since the advent of excretory urography one group of physicians advocates diagnosis on the basis of excretory urography alone. Others favor cystoscopic examination but differ on the amount of examination of each kidney and on indications

* Read April 17, 1940 before the Section of Genito-Urinary Surgery of The New York Academy of Medicine

for retrograde pyelography Opinion varies between members of the extremely radical school who advocate excretory urography alone with no instrumentation and those of the ultraconservative school who insist on multiple cystoscopic examinations if they are necessary, routine bilateral retrograde pyelograms in all cases and examination of ureteral specimens of urine from both kidneys by wet smear, acid-fast stain and inoculation into guinea pigs

It is my purpose in this paper to determine if possible the current trend in diagnosis in renal tuberculosis and if possible to evaluate the comparative accuracy of the various methods of diagnosis If this can be done, possibly certain principles in diagnosis will be brought out that will simplify the subject, especially for teaching purposes The basis for this study is 216 cases of proved renal tuberculosis that have been encountered at The Mayo Clinic during the past five years The cases are almost consecutive In the first 100 cases all cases of proved renal tuberculosis were included This series has been reported in an earlier paper written in collaboration with Braasch In the remaining 116 cases no case was included in which nephrectomy had been previously performed for renal tuberculosis This was done so that the study might more nearly mirror the initial diagnostic problem as the patient first consults his physician From the data obtained it was apparent that our methods of diagnosis in renal tuberculosis have been altered considerably in recent years

In making such a study the practical aspects must be foremost and the problem must be viewed in its larger aspects Details and controversial points of academic interest only, must assume the background For instance, it is not pertinent to such a study whether or not all renal tuberculosis is bilateral, whether or not tuberculous lesions of the kidney heal or whether or not in an occasional case tubercle bacilli, demonstrated in a ureteral specimen of urine, could have been picked up by the ureteral catheter as it passed through the bladder into the ureter The diagnostic procedures at hand, imperfect though they may be, must be accepted and conclusions must be drawn accordingly For the purpose of brevity in the remainder of this paper I shall speak of the involved or the more involved kidney as the "bad" kidney The uninvolved or least involved of the two kidneys will be designated the "good" kidney

In the analysis of such a problem certain premises must form a basis on which to build The following statements are generally accepted,

and will serve as the premises of this paper 1 Tubercle bacilli are not excreted from a normal kidney 2 Sound diagnosis consists in employing adequate diagnostic procedures to supply sufficient information to insure proper treatment Fewer procedures are insufficient More procedures than this are not in the interest of the patient either physically or economically This is especially true with regard to instrumentation and anesthesia 3 The clinical term "unilateral renal tuberculosis" is inaccurate as there is no clinical method by which 1 kidney can be proved to be free from tuberculosis The four methods of investigating a kidney in the presence of this disease are (1) excretory or retrograde urography, (2) microscopic examination of a ureteral specimen of urine, (3) acid-fast staining of 1 ureteral specimen of urine, and (4) inoculation of a guinea pig with a ureteral specimen of urine Although all of these methods are extremely valuable, none are infallible and it is well known that the results of all may be negative even though tuberculosis is present in a kidney It would be better, therefore, to employ the general term "renal tuberculosis" and to specify the condition of each kidney, stating the type of investigation used to arrive at the diagnosis 4 The weight of evidence suggests that catheterization of a tuberculous kidney (if carefully done) for the purpose of obtaining a specimen of urine for examination is a fairly safe procedure Danger of infecting the "good" kidney in this manner is minimal or almost nil 5 Experience and a perusal of the literature suggest that a retrograde pyelogram of a kidney with an open tuberculous lesion may initiate dissemination of the disease, the most common type of dissemination mentioned in the literature is "tuberculous meningitis" Cases of meningitis following nephrectomy for renal tuberculosis may be the result of the pyelogram before operation rather than the trauma incidental to the operation Although the danger of retrograde pyelography has been minimized considerably since it has become almost routine to employ media containing organic iodine (as is used in excretory urography), rather than sodium iodide, there is still a definite though small risk accompanying it

A review of the 216 cases studied elicited some interesting data In approximately 71 per cent of these cases acid-fast staining of the vesical urine demonstrated tubercle bacilli, this finding suggests that in at least 75 per cent of cases the history, symptoms, physical examination and examination of the vesical urine (properly collected) should establish the presence of tuberculosis of the urinary tract The problem in the

majority of cases, therefore, is not so much one of determining the presence of renal tuberculosis as it is of determining which kidney is infected or, if bilateral, the degree of involvement of each kidney. Experience at The Mayo Clinic over a period of many years makes us feel that the presence of tubercle bacilli in the urine is indicative of renal tuberculosis and does not occur with any appreciable frequency in genital tuberculosis.

The relative frequency of the various diagnostic procedures employed is of interest. Cystoscopic examination was carried out in 87 per cent of cases and excretory urography in 90 per cent. Diagnosis was made solely on the basis of excretory urography and examination of the vesical urine in 12.8 per cent of cases. In these latter cases supplementary diagnostic methods were not employed because in most of them advanced bilateral tuberculosis could be diagnosed easily from the excretory urogram, in a few, catheterization of the ureters was impossible owing to an impassable ureteral stricture. Catheterization of the ureters to obtain specimens of urine for examination was carried out on either one or both sides in 76.3 per cent of cases. The "good" kidney was catheterized in 67.4 per cent of cases and the "bad" kidney in 46.7 per cent. Retrograde pyelography was employed in only 26 per cent of the 216 cases, retrograde pyelograms of the "good" kidney were made in 11 per cent of cases and of the "bad" kidney in 19 per cent. In only a very occasional case was cystoscopic examination performed more than once for diagnosis. These figures suggest that the trend in diagnosis is swinging toward excretory urography and away from retrograde pyelography, that not more than one cystoscopic examination of as brief duration as possible is being employed in each case and that ureteral catheterization is still employed for the purpose of obtaining specimens of urine for examination in a large percentage of cases.

The reason for this trend in diagnosis may be more fully explained by a more detailed study of these cases. As far as the "bad" kidney is concerned, if the bacillus of tuberculosis has been demonstrated in the vesical urine, detailed visualization in the excretory urogram is not extremely important. By this statement I mean that in the majority of cases the diseased kidney, or at least the more involved of the two, can be determined readily from the excretory urogram. When this fact has been ascertained, nothing more from the standpoint of diagnosis is obtained by attempting to visualize every minute detail by filling and dis-

tending the kidney with media by retrograde pyelography. It must be remembered that diagnosis of renal tuberculosis by excretory urography is somewhat different from that by retrograde pyelography. In a case in which renal tuberculosis is known to be present, as demonstrated by examination of the vesical urine, diagnostic procedures do not need to be pushed to the bitter end in order to demonstrate the pyelographic deformity of cortical necrosis so glibly described in urologic textbooks. A careful examination of the excretory urograms in this group of cases demonstrated the fact that the irregular feathery outline typical of necrosis was by no means the most common finding in the excretory urogram. For instance, of ninety-five "bad" kidneys in which tuberculosis was proved to be present, the excretory urographic findings in order of frequency were as follows: (1) absence of visualization (in 35 per cent of cases), (2) delay in visualization (in 25 per cent of cases), (3) caliectasis, (4) evidence of necrosis, (5) cicatricial deformity and isolation of the tips of calices, (6) deformity and dilatation of the ureter and (7) pyelectasis.

If these facts are kept in mind, the routine use of bilateral retrograde pyelograms in every case of renal tuberculosis may be classed as an excessive and unnecessary diagnostic procedure that is not in the interest of the patient and does not supply sufficient information to justify its use. If a retrograde pyelogram is necessary for diagnosis, however, it is of course a perfectly justifiable procedure. This will be more fully considered later in this paper. Figures 1 and 2 illustrate the fact that complete visualization is not always necessary. In both of these cases tuberculosis had been demonstrated by examination of the vesical urine, previous to urographic examination. In Figure 1 there is marked delay in visualization of the left kidney. Visualization is incomplete but there is marked dilatation of the calices. The right kidney is fairly well outlined and is probably normal. In Figure 2 similar findings are present. It is obvious that a left retrograde pyelogram in either case is entirely unnecessary.

In the case of the "good" kidney the problem of diagnosis is somewhat altered. For this kidney, detail in urographic visualization is considerably more important than it is in the "bad" kidney. In some cases visualization by excretory urography will be sufficiently good to enable the physician to describe the kidney as "urographically normal." In others the visualization may be almost complete, yet the tip of a calix may be indistinct.

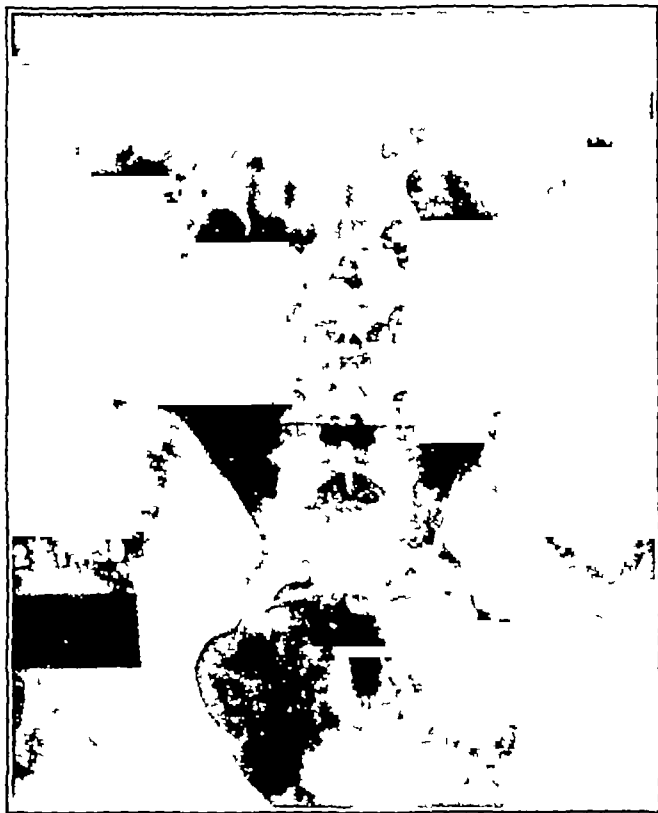


Fig 1—Excretory urogram revealing left renal tuberculosis

These are usually described as “probably normal.” In the remainder the kidney is too incompletely outlined for an opinion. The question then arises as to just how normal are the kidneys that are described urographically as “normal” or “probably normal.” In 121 of the 216 cases in the series, the “good” kidney was described by the urologist from the excretory urogram as “normal” or “probably normal.” Ureteral specimens of urine were obtained from ninety-two of these 121 kidneys. In twenty-four cases pyuria (more than 3 leukocytes per high power field in the centrifuged specimen) was found to be present. Twenty-six per cent of the ninety-two kidneys catheterized were demonstrated to be involved with tuberculosis either by the acid-fast stain or inoculation of guinea pigs. These findings are significant as they demonstrate that catheterization of the “good” kidney to obtain a specimen of urine for examination is highly important if any degree of accuracy in diagnosis is to be obtained. It also illustrates the fact that diagnosis by



Fig 2—Excretory urogram revealing left renal tuberculosis

excretory urography alone, as advocated by the radical school, is not accurate diagnosis. Whether or not the results of treatment following such an inaccurate diagnosis are good enough to justify employing this method of diagnosis will be considered later in this paper.

Although retrograde pyelography is becoming less important in diagnosis of renal tuberculosis, it still has an important and valuable place. In cases in which the "good" kidney is not visualized sufficiently by excretory urography, it may be necessary to employ retrograde pyelography in conjunction with examination of the ureteral specimen of urine in order to give an accurate opinion concerning the status of the kidney. Just how often this is necessary is open to question. After reviewing the films in this series of cases I am left with the impression that it is not necessary as often as I previously had supposed. For instance, only seven retrograde pyelograms had been made to supplement the excretory urograms of the sixty-nine "good" kidneys in the first 100 cases of this series. At first glance this seems to be entirely

too few, which it may be, and yet a careful comparison of these films with the excretory urograms revealed that a surprisingly small amount of additional information was supplied by them. If the "good" kidney is outlined reasonably well in the excretory urogram, the impression is gained that excretory urography plus examination of the catheterized ureteral specimen of urine gives a remarkably accurate diagnosis. If visualization of the "good" kidney is not good, however, retrograde pyelography is entirely justifiable.

One must remember that up to this point the discussion so far in this paper has concerned primarily the cases in which the diagnosis of renal tuberculosis is relatively simple and is usually made at the initial examination. This comprises roughly about three-fourths of the cases. In the remainder the diagnosis may be difficult, and it may be necessary to employ all methods of diagnosis, including bilateral retrograde pyelograms, to establish an accurate diagnosis. This is especially true in cases of minute early lesions.

From what has been said up to this point certain conclusions may be drawn concerning the accuracy of the various methods of diagnosis. The study suggests that excretory urography will reveal which is the "bad" kidney in a large percentage of cases. In this regard it is very accurate though this information may be supplemented, if necessary, by examination of the ureteral specimen of urine. The excretory urogram will usually suggest the status of the "good" kidney, but here it is inaccurate and inadequate and should be supplemented by catheterization of the kidney, by microscopic examination, acid-fast stain and by inoculation of guinea pigs with the ureteral specimen of urine. This combination of diagnostic methods will yield highly accurate information regarding the "good" kidney, although at times retrograde pyelography is indicated. Bilateral retrograde pyelograms are necessary only in a limited group of cases in which it is difficult to demonstrate the presence of tuberculosis or those cases in which the renal lesions are extremely early or very minute. One cystoscopic examination should be sufficient for diagnosis except in the occasional case. Multiple cystoscopic examinations should be avoided.

Now that the comparative accuracy of our various diagnostic methods has been evaluated, one wonders how accurate diagnosis should be in order to advise proper treatment, or to put the question another way, what preoperative findings should be present before nephrectomy

for renal tuberculosis is advised. This question is not easily answered, for it involves a personal equation both of the physician and patient and requires observation of results of treatment over a period of many years.

In an effort to clarify this subject somewhat Kibler and I made an exhaustive follow-up study of all patients who had undergone nephrectomy at the clinic from 1912 to 1932 inclusive. The results were studied from the standpoint of the findings obtained from investigation of the "good" kidney prior to operation. The results of this study have been fully reported elsewhere, but a few of the more pertinent findings may be mentioned briefly. It was found that 1,131 patients had been subjected to nephrectomy because of renal tuberculosis. These cases were divided into artificial groups depending on the results of the preoperative investigation of the "good" kidney. No attention was paid to the condition of the "bad" kidney, to the length of time the disease had been in progress, or to associated disease, tuberculous or non-tuberculous, elsewhere in the body. It was felt that in creating the artificial groups, these other factors would be fairly equally distributed and would not affect the comparative results. Four large groups were created. In group 1 the "good" kidney was not catheterized. In the remaining groups the "good" kidney was catheterized to obtain a specimen of urine for examination. Group 2 indicates that the centrifuged ureteral specimen of urine contained no pus cells or at least less than 3 leukocytes per high power field. In group 3, three to ten leukocytes were found per high power field. In group 4 there were more than ten leukocytes per high power field.

Groups 2, 3 and 4 were further subdivided with regard to the results of acid-fast staining and guinea pig inoculation of the ureteral specimen of urine. Early in the study it became apparent that a negative acid-fast stain of a ureteral specimen of urine was of little significance. Therefore, the subdivisions A, B and C are on the basis of positive acid-fast stains and positive and negative guinea pig inoculation. Subdivision A indicated that no positive acid-fast stains were obtained and guinea pig inoculation was not carried out. Subdivision B indicated that no positive acid-fast stains were obtained and that guinea pigs were inoculated and the results proved to be negative. Subdivision C indicated that positive acid-fast stains or positive results of guinea pig inoculation or both were obtained. In Table I a few of the more

TABLE I

RESULTS OF NEPHRECTOMY IN CASES OF RENAL TUBERCULOSIS
 CASES GROUPED ACCORDING TO TYPE OF INVESTIGATION
 EMPLOYED AND FINDINGS OBTAINED PREOPERATIVELY
 IN THE "GOOD" KIDNEY

Years After Operation	Group *	Patients Traced		
		Number	Living Per Cent	Cured or Improved, Per Cent
5	4	45	66.6	44.4
	3	108	56.5	40.8
	2	718	79.7	65.2
	2C	55	58.2	36.4
	2B	209	86.7	75.2
10	4	25	44.0	44.0
	3	87	48.3	39.1
	2	522	65.2	56.4
	2C	30	33.3	30.0
	2B	113	72.6	65.5

* Group 4—Ureteral specimen of urine contained more than 10 leukocytes per high power microscopic field

Group 3—Ureteral specimen of urine contained 3-10 leukocytes per high power microscopic field

Group 2—Ureteral specimen of urine microscopically negative (0-3 leukocytes per high power field)

Group 2C—Ureteral specimen microscopically negative. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both

Group 2B—Ureteral specimen of urine microscopically negative. Results of guinea pig inoculation and acid-fast staining negative

important groups and subdivisions have been compiled for comparison. It is interesting to note that the more "negative" the "good" kidney is proved to be, the better are the results following nephrectomy. Groups 4, 3, and 2 C contained too few cases to be of statistical value, but they illustrate well the higher mortality and lower percentage of cures when involvement of the "good" kidney can be demonstrated even though the lesion may be minute or extremely early. The best results of course were obtained in group 2 B, which comprises the cases in which no pus was being excreted from the "good" kidney and results of guinea pig inoculation proved to be negative.

TABLE II

LENGTH OF SURVIVAL IN RENAL TUBERCULOSIS CASES IN WHICH NEPHRECTOMY WAS PERFORMED AND THOSE IN WHICH NO OPERATION WAS PERFORMED BECAUSE OF DEFINITE BILATERAL DISEASE

Years After Operation or Diagnosis	Renal Tuberculosis							
	Bilateral No Operation Patients Traced*		Results of Nephrectomy in a Series of 1131 Cases (1912-1932 Inc.) † Patients Traced					
			Total Series		Group 2 ‡		Group 2B	
			Number	Per Cent Living	Number	Per Cent Living	Number	Per Cent Living
5	118	58.1	1016	71.9	718	79.7	209	86.7
10	133	26.3	753	59.9	522	65.2	113	72.6
15	88	15.9	513	48.9				
20	38	7.1	251	40.3				

* Data collected by Braasch and Sutton

† Reported previously by Emmett and Kibler

‡ Group 2—Ureteral specimen of urine microscopically negative (0-3 leukocytes per high power field)

Group 2B—Ureteral specimen of urine microscopically negative Results of guinea pig inoculation and acid-fast staining negative

If the ureteral specimen of urine from the "good" kidney is microscopically negative, the question is often asked if it is necessary to await the results of guinea pig inoculation before proceeding with removal of the "bad" kidney. To answer this question reference should be made to group 2 C. These are the cases in which the specimen of urine from the "good" kidney contained no pus, but results of guinea pig inoculation proved to be positive. It will be seen that the results in these cases were poor and yet 30 per cent could be classified as cured or improved ten years after operation. The percentage of ten-year survivals in this group, however, is not much better than in those cases of grossly bilateral renal tuberculosis reported by Braasch and Sutton in which no surgical treatment was carried out. The percentage of ten-year survivals in this series was 26.3 (Table II). When the results of operation in renal tuberculosis are being estimated, the results which might have been obtained if no operation had been performed must always be taken into consideration. The answer to this question, there-

TABLE III

RESULTS OF NEPHRECTOMY IN CASES OF GROSSLY BILATERAL RENAL
TUBERCULOSIS IN WHICH THE MORE INVOLVED OF
THE TWO KIDNEYS WAS REMOVED

Years After Operation	Group *	Traced Patients		
		Number	Living Per Cent	Cured or Improved, Per Cent
5	3C	15	46.7	20
	4C	12	33.3	0
10	3C	10	40.0	20
	4C	6	00.0	0

* Group 3C—Urteral specimen of urine contained 3-10 leukocytes per high power microscopic field. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both.

Group 4C—Urteral specimen of urine contained more than 10 leukocytes per high power microscopic field. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both.

fore, is a personal matter between the surgeon and his patient. The patient can be advised as to the prognosis and decide whether or not he feels the chances of cure or improvement warrant operation. Most patients prefer to submit to nephrectomy under these circumstances and it is, therefore, probably a justifiable procedure to go ahead with operation without waiting for the results of the animal inoculation. Even if such a course is pursued, however, the guinea pig inoculation should be done to permit a more accurate prognosis and to assist in deciding on the type of postoperative care to be given the patient.

When there is a definite open lesion in the "good" kidney which is excreting pus cells and tubercle bacilli, the results of surgical treatment have been extremely poor. This is especially true if any urographic deformity can be demonstrated. In Table III the results in this type of case are given. Occasionally a patient is seen who has bilateral renal tuberculosis and such pronounced vesical symptoms that the surgeon feels removal of the worst kidney may give some relief. Experience at the clinic with this type of surgical procedure is extremely discouraging and we feel that it should be avoided whenever possible.

Referring again to the inaccuracy of the clinical use of the term "unilateral renal tuberculosis," Table I is of especial interest. It would

depend on the school of thought to which one adheres, which of these groups should be classified as "unilateral renal tuberculosis." For instance, the radical school, which depends almost entirely on excretory urography for diagnosis, might include all of these groups under the term "unilateral," whereas the ultraconservative school would speak only of cases in group 2 B as unilateral. From the postoperative results, it is apparent that even group 2 B contains cases in which tuberculosis must have been present at the time of diagnosis, even though it was not detected. If larger groups of cases throughout the country could be studied from this point of view and the data pooled, the information obtained would be invaluable. The process of teaching the medical student would certainly be simplified, for he could be taught the relative accuracy of the various methods of diagnosis, and the average results of treatment that might be expected depending on the type of investigation and findings obtained. With such information he could then rely on his own judgment and with confidence and self-assurance decide on methods of diagnosis and treatment rather than follow with blind faith the dogma of his instructor. It must be remembered, of course, that treatment in any disease can never be determined automatically by reference to statistical tables after diagnosis has been completed. Each case must be individualized and the physician must temper his judgment with such factors as the general condition of the patient, the length of time the disease has been in progress and the presence or absence of associated diseases.

SUMMARY

Sound diagnosis in any disease implies that adequate diagnostic procedures have been employed to obtain sufficient information to insure proper treatment. Fewer procedures than this are insufficient. More procedures are not in the interest of the patient either physically or economically. An analysis of the methods of diagnosis employed in 216 cases of renal tuberculosis encountered at the clinic in the past five years suggests that the trend of diagnosis is away from retrograde pyelography and toward excretory urography. An appraisal of the various methods of diagnosis employed in these cases suggests that in the majority of cases accurate diagnosis can be made by means of excretory urography and one cystoscopic examination for the purpose of obtaining specimens of urine from the good kidney and at times both

kidneys to be examined microscopically as a wet smear, with the acid-fast stain and by inoculation into guinea pigs. It is seldom necessary to perform more than one cystoscopic examination on each patient. Multiple cystoscopic examinations are to be avoided. Retrograde pyelograms of the "good" kidney may be indicated when visualization by excretory urography is not adequate. In the average case retrograde pyelograms of the "bad" kidney are not necessary even though visualization by excretory urography is incomplete or absent. There is a small group of cases, however, in which the diagnosis of renal tuberculosis is difficult and in these cases bilateral retrograde pyelograms must be employed. The routine use of bilateral retrograde pyelography in every case of suspected renal tuberculosis is to be condemned as an unnecessary diagnostic procedure which is not in the interest of the patient.

With the comparative accuracy of the various diagnostic procedures evaluated, an attempt has been made to answer the question of how accurate diagnosis must be and what findings must be obtained in renal tuberculosis to assure satisfactory results from nephrectomy. A brief summary of the late results in 1,131 cases of renal tuberculosis in which nephrectomy was performed was used as the basis on which to answer this question. The study was based on the type of investigation used and the findings obtained in the preoperative investigation of the "good" kidney. The study demonstrates the inaccuracy of the clinical term "unilateral" renal tuberculosis and illustrates the fact that the more "negative" the "good" kidney is proved to be, the better is the prognosis for the patient following nephrectomy. The study emphasizes the need for accurate diagnosis in each case to enable the physician to give the patient a fairly accurate prognosis and to decide on proper preoperative and postoperative care. From the tabulated results of a large series of cases such as is presented herein, physicians should be better able to judge in which cases nephrectomy is justifiable. If more cases from large clinical centers could be studied from this point of view and the results pooled into one tabulation the information would be of still greater value.

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THE TREATMENT OF RENAL TUBERCULOSIS*

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THE treatment of renal tuberculosis is an important subject because of its public health aspects as well as its general medical considerations. When we know that not less than a million and a half people have active tuberculosis, of whom, most conservatively, 5 per cent have renal involvement, the magnitude of the problem of furnishing adequate medical care is apparent.

The public health interest lies in controlling the tremendous economic loss incurred through deaths and physical disabilities incident to this disease. Let us take a rapid survey of the vital statistics and medical facilities available for the treatment of this condition. To begin with, many of our larger centers of population do not have vital statistics which furnish accurate data concerning the incidence or death rate of renal tuberculosis. One municipal tuberculosis sanatorium in one of the most important cities in our country cannot report the incidence of renal tuberculosis nor its death rate because of lack of resources. Many of the health departments have no definite policies in regard to the method of handling cases of renal tuberculosis. The census reports of deaths due to renal tuberculosis are only as accurate as the local reporting of the disease and these are very variable.

The United States Public Health Service and the Social Security Administration, both of which are cognizant of conditions, have comprehensive plans to furnish adequate medical care for tuberculous patients which it is hoped will carry along with it adequate urological care.

The Social Security Program is estimated on a cost basis as follows:

- | | | |
|---|--|---------------|
| 1 | For construction of 79,515 hospital beds at \$3,500 per bed | \$275,302,500 |
| 2 | For annual maintenance of 79,515 hospital beds | 59,636,250 |
| 3 | For x-ray examination of family contacts of 862,596 known cases of tuberculosis at \$7.00 each | 6,038,172 |

* Read April 17, 1940 before the Section of Genito-Urinary Surgery of The New York Academy of Medicine.

The report of the Technical Committee on medical care to the National Health Conference which was held in July, 1938, had the following plan presented by the Public Health Service

Construction	\$15,000,000
Three years maintenance	6,000,000
Annually available for other elements of the tuberculosis program	43,000,000

These figures show how important the Social Security and Public Health authorities consider the problem of medical treatment for tuberculosis patients. We should make it our duty to interest ourselves in this problem and bend every effort to control a disease which is so great an economic drain on our country.

The general medical-surgical consideration of the treatment of renal tuberculosis calls for a comprehensive understanding of many factors which are involved in each case. The following factors should be taken into consideration and appropriate measures taken

- 1 Extent of renal process
 - a Miliary
 - b Necrotic destructive
 - c Nephritic
- 2 Extent of extrarenal lesions
 - a Bilateral involvement
 - b Bladder involvement
 - c Genital involvement
 - d Pulmonary
 - e Other extraurinary lesions
- 3 Factors affecting general resistance
 - a Economic
 - b Psychologic
 - c Climatic—ultraviolet
 - d Pain
 - e Coexisting bacteriuria
 - f Food
 - g Medication, tonics

EXTENT OF RENAL INVOLVEMENT

Whether the condition is (1) one of tuberculous nephritis, which should be interpreted as indicating non-destructive minimal lesions, (2) destructive parenchymatous or (3) acute disseminated miliary is

the first consideration. The tuberculous nephritic patients should be treated medically, and all measures to conserve and build up the general resistance instituted. The destructive parenchymatous lesions are the ones which call for our keenest judgment. The destructive parenchymatous processes which involve any more tissue than one minor calyx should be subjected to nephrectomy, unless there are serious contraindications to surgery from a risk standpoint. The patient with a slight involvement of one minor calyx is our greatest problem—should nephrectomy be performed or should he be subjected to medical regime? This depends of course upon whether renal tuberculosis heals. There seems to be no sound reason for maintaining that tuberculosis does not heal. Tuberculous processes heal in every other tissue. The cures of the nephrectomized patients run well above the known incidence of bilateral involvement. I have observed patients of my own with involvement of solitary kidneys in whom the tuberculous process has become arrested. In the absence of special indication, the minimal lesions in single calyces should be treated with rest and building up of resistance. The acute miliary lesion should not be treated surgically because it is bilateral and usually a terminal fatal process.

EXTENT OF EXTRARENAL LESIONS

Bilateral destructive lesions usually call for medical treatment. In instances in which one side is extensively involved and productive of appreciable distress and the other side has minimum involvement, nephrectomy of the bad kidney is indicated.

When the bladder symptoms are severe and progressive, nephrectomy is indicated. Persisting bladder symptoms call for the following treatment, in order of relative risk: urinary antiseptics for mixed infections, caprokol, when tolerated and effectual, increasing strength of phenol lavage, when effective, up to 6 per cent, intrathecal alcohol injections, presacral neurectomy, ureterostomy, ureterosigmoidostomy.

When genital involvement coexists, these lesions should be treated with medical measures until they become destructive at which time they should receive appropriate surgical treatment. There does not seem to be justification for early extensive removal of the seminal tract.

When pulmonary involvement exists, appropriate measures should be instituted. There is no objection to keeping the open pulmonary patient with other open cases but it is not justifiable to put patients with

closed lesions with open ones, which is unfortunately frequently done. Osseous, glandular and gastrointestinal lesions call for appropriate treatment and modify our advice in the renal problem. Tuberculosis of the central nervous system is always fatal and usually rapidly so.

GENERAL RESISTANCE

The general resistance factor is the vital influence, as it is this factor which determines the course of each case. Every effort should be made to influence the general resistance favorably. The Social Security Administration is interested in improving the economic status of masses of the people. Our first interest then should be directed to improving the general living conditions both collectively and individually.

The individual who is the breadwinner will not and in many instances cannot be taken out of circulation with our present economic setup. The psychological factors are important in progress, in that a depressing psychological status retards recovery. The importance of this factor should not be minimized and real effort should be devoted to psychic treatment.

The climate is important. In the Southwestern states and Central American countries the incidence is low for genitourinary tuberculosis, and Dr. Boyd, the present President of Panama, states that there is no genitourinary tuberculosis in Panama. Whenever possible patients should be put in an advantageous position by living in these climates both before, during and after surgery. Ultraviolet radiation in conservative dosage is good when pulmonary involvement does not exist.

The question of diet is very important. Cod liver oil, plain, if tolerated, or its concentrate, if not, with at least one quart of milk a day should be given in conjunction with a generally wholesome diet.

Coexisting infections of the kidney and bladder are more effectively combated now than ever before. Nearly all bacteria except the *Streptococcus fecalis* respond to the sulphones, and mandelic acid is equally effective on all except the *Escherichia coli*. Control of the complicating infections makes the difference between comfort and discomfort and between improvement and retardation.

Bed rest is of paramount importance both before and after surgery, if surgery is done, and the amount of bed rest should be judiciously directed to suit the indications in the individual case.

Sanatorium or equally satisfactory housing care with abundant rest

should be provided for all patients for at least a year following nephrectomy or until there is indication of cessation of activity of the lesion which is being treated medically

CONCLUSION

All effort possible should be expended in making available adequate facilities for treating renal tuberculosis in order to materially lessen the incidence and mortality

Bed rest and the many details utilized in building resistance with or without and before and after surgery are the most important single factors in the treatment of renal tuberculosis

today be adequately handled. Unfortunately, only a few of us have access to the necessary laboratory facilities.

There is no one reliable provocative test which can be relied upon to produce positive laboratory evidence in cases of latent infection. Handling the cervix, or local application of any irritating material such as glycerine or silver nitrate, may provoke a discharge of latent gonococci.

Unfortunately, complement fixation tests are of little or no value in making a diagnosis, although a strongly positive complement fixation test which becomes negative as symptoms disappear, suggests a cure. If the test remains positive under similar circumstances, it may be regarded as suggestive evidence that gonococcal infection still remains.

As we look back on the methods of treatment only recently in vogue, we must realize that none of them could possibly have had any real curative value. In acute urethritis we were careful to avoid treatments that risked spreading the infection to the cervix. If an acute endocervicitis developed, strong antiseptics were avoided lest the tubes become involved. As the infection subsided, antiseptics were applied to the cervical mucosa. On reflection, we realize that gonococci invariably live in the depths of and beneath the mucosa, and that no applications to the surface can possibly reach them in their habitat. The risk of spreading gonococcal infection to the tubes by trauma of the mucosa in the name of treatment contraindicates the use of local antiseptic applications. With modern chemotherapy the cervix usually improves so rapidly that there would be no place for local treatment even if it were beneficial.

Vaginal douches can do nothing more than wash out the offensive secretions from the vaginal vault. As treatment, douches are comparable to the use of a handkerchief in a case of acute rhinitis. It is true that the warmth engendered in the pelvis by the use of hot douches often renders patients with acute salpingitis more comfortable.

The use of the Elliott apparatus or diathermy constituted an improvement on the douche in bringing heat to the pelvic structures. Both undoubtedly gave relief from pain and often hastened resolution in cases of tubal infection. It is noteworthy that the Strong Memorial Hospital in Rochester, where they were in constant use, has abandoned them entirely for chemotherapy.

A host of other non-surgical methods of treatment have been tried

and found wanting. Among them I may mention Gellhorn's non-specific protein therapy for subacute salpingitis, iontophoresis and vaccines. The latter will produce a positive complement fixation test but does not cure or improve gonococcal infections.

In the treatment of non-specific cervicitis, the use of a cautery is of the greatest value. It cannot be too strongly emphasized that its use in gonococcal infections is illogical and unpardonable. It is true that linear cauterization will decrease the amount of mucopurulent discharge. It cannot possibly destroy all the gonococci which thrive between the areas of coagulation. The danger of producing an extension of a localized infection to the tubes far outweighs the possible benefits of symptomatic relief. No endocervix should be cauterized while gonococci are demonstrable. Use of the cautery in secondary infections after gonococci have been eliminated is often most helpful.

For a long time we have realized that endocervical gonococcal infections tend to die out in 6 months or less if tubal infection does not intervene. In an effort to determine this point, Mahoney selected a group of sixty imprisoned prostitutes, in all of whom positive spreads and cultures could be obtained from the cervix. Laboratory determinations were made every 48 hours. At the end of 40 days, all spreads and cultures in the entire group were negative, although no treatment of any kind had been given. It is evident to me that in the past we have credited our methods of treatment with the cure of patients who were, in reality, all curing themselves. I firmly believe that they recovered, not because of our interference, but in spite of it. At present we use no local treatment whatever, but rely on sulfapyridine or sulfathiazole to cure our patients.

TREATMENT

The only generally recognized curative methods of treatment of gonococcal endocervicitis and salpingitis at our disposal are

- 1 The use of artificially produced fever, or better
- 2 Appropriate sulfonamides given in adequate amounts

The Kettering hypertherm apparatus or its equivalent was the positive method of treatment par excellence only a few years ago. A high percentage of cures can be, and undoubtedly have been, produced by this method. Unfortunately, hyperthermia is time-consuming, uncomfortable and expensive for the patient, as well as dangerous, if not ad-

ministered under the constant supervision of a carefully trained staff. It now finds its place in the treatment of cases in which the sulfonamides have failed to cure. Its value in the treatment of gonococcal arthritis is probably as great as that of the sulfonamides. In the Rochester Clinic, where hyperthermia was in constant use only recently, it has been abandoned, except for use in the sulfonamide failures. In these cases it is often of great value.

SULFONAMIDE TREATMENT

While excellent results were obtained by treatment with sulfanilamide as evidenced by reports of series of cases with a rate of cure varying from 30 per cent to 90 per cent² or more, the better results are only obtainable with patients kept under most careful supervision in the hospital. Fractional administration of the drug during day and night were necessary, and the frequent production of toxic symptoms made adequate sulfanilamide treatment a nightmare for both patient and physician.

If ambulatory treatment was attempted, it usually met with very unsatisfactory results. Fear of, or the actual development of toxic symptoms, prompted the physician to reduce the dose of sulfanilamide to the point of easy tolerance. As a rule, patients were rather rapidly relieved of their clinical symptoms, gonococci could not be demonstrated by laboratory methods, and the case was only too often pronounced cured before a relapse made him or her an uncomfortable menace to society. It is estimated that not more than 30 per cent of ambulatory patients were cured with sulfanilamide. Sulfanilamide has no longer a place in the treatment of gonococcal infections, except for a very limited field in treating cases which have not been cured by other much more potent preparations, i.e., sulfapyridine or sulfathiazole.

Since sulfapyridine became available, an increasing number of enthusiastic reports on its efficacy in gonococcal infections have appeared. The fact that the drug can produce all the toxic symptoms resulting from large doses of sulfanilamide, plus serious kidney complications, at first greatly decreased its sphere of usefulness.

Studies by Mahoney and Van Slyke of the U. S. Public Health Department, and various other clinics, have shown that sulfapyridine, if given for from 10 to 12 days in divided doses of 0.5 gram every 4 hours,

² Nimelmann et al.² and Dougl.¹ report 94 per cent cures.

four times daily (not exceeding a total daily dose of 2 grams) is not commonly toxic. Serious toxic symptoms resulting from such doses are extremely rare. Moreover, the percentage of cures arrived at by this treatment is almost as high as that resulting from dangerously large doses.

Patients treated in the manner just described must be impressed with the extreme importance of taking their tablets regularly at the hour advised. Neglect of this particular, courts failure. While taking the drug in this way, hospitalization is unnecessary, and there is no need to limit fluid intake.

During the course of treatment, we make it a rule to give patients only eight tablets at a time, enough to last for 2 days. The patients are seen and examined at 48 hour intervals. If toxic symptoms are encountered, or if anuria, hematuria or renal pain should develop, treatment must be stopped.

Ordinarily, cases of gonococcal endocervicitis under the treatment that we are discussing will show obvious improvement in from 48 to 96 hours. The purulent discharges decrease very quickly. The cervix, which is usually red and swollen, rapidly assumes a normal appearance. It is uncommon to find either positive spreads or cultures after 48 hours of treatment. If no improvement is evident after 5 or 6 days, the drug should be stopped for a few days and a change made to sulfathiazole. The latter is administered in the same dosage as is sulfapyridine. Frequently, patients appear entirely well by the end of 4 or 5 days. Even if this be the case, treatment should be continued until it has been given for 10 or 12 days. We have regularly insisted on having our patients continue for 12 days. The results are usually so extraordinary that the physician who is familiar with the ordinary course of gonococcal infections can hardly believe the clinical evidences of improvement and cure.

When the dosage of sulfapyridine is kept below 2 grams per day, serious toxic symptoms rarely develop. Mild headaches, anorexia or slight nausea are frequent, but do not often necessitate cutting short the treatment. Blood counts and urine analyses made at each visit are a safeguard, although some clinics have dispensed with them without disastrous results.

Blood concentration studies are of interest for the purposes of making scientific studies. They are not necessary for the ordinary

practical treatment of patients. With a daily total of 2 grams of sulfapyridine or sulfathiazole, every patient studied has absorbed enough of the drug to be effective. A certain amount of variation of the concentration of the drug has been found, but in repeated studies it has not been possible to find any relationship between cures and blood concentration when this level of drug intake has been maintained.

TOXICITY

All of us are familiar with the possible toxic effects that may result from the administration of sulfapyridine. In treating 200 hospitalized males with rather large doses of sulfapyridine, Mahoney found that only 10 per cent were free of any toxic symptoms and that about 7 per cent or 8 per cent of these cases might be rated as "severe." In studying 100 patients who received 3 grams of sulfapyridine on the first day and 2 grams on the subsequent days of treatment, about 60 per cent showed some slight evidence of toxicity, three developed severe headaches and one, severe nausea. Among the milder evidences of toxicity, Mahoney lists insomnia (15 cases), anorexia (15 cases) and mentions other symptoms of relative unimportance. One patient had an idiosyncrasy to the drug which necessitated stopping treatment. In only this one patient, among the 300 patients treated, was it necessary to stop therapy on account of toxicity.

In treating 650 women with gonococcal infections at the New York City House of Detention, Nimelmann has given the usual dose of 2 grams daily for 8 days. In this series there have been a few toxic manifestations, including slight headache, nausea or occasional vomiting. There have been no renal disturbances caused by the drug and no critical blood dyscrasias.

Using larger doses of sulfapyridine (5 grams for 3 days and 3 grams for 4 days) E. D. Barringer, Horowitz and Strauss were obliged to stop treatment on account of toxic symptoms in 12 of a group of 100 patients so treated.

In our own limited experience, patients given doses of 2 grams of sulfapyridine per day are often conscious of some mild sensations such as sleepiness, faintness, anorexia, which do not warrant stopping therapy. One private patient bought her own sulfapyridine and did not return for observation. She took 5 grams daily for 10 days before returning to us cured of gonococcal infection but suffering from violent gastro-

intestinal symptoms

Patients treated with sulfapyridine commonly develop a relative monocytosis while the hemoglobin and red count usually show only minor variations. It is inadvisable to treat patients with sulfonamides in whom the hemoglobin figure is below 50 per cent. It should be mentioned that pregnancy is not a contraindication to the use of the sulfonamides.

RESULTS OF TREATMENT WITH SULFAPYRIDINE

Ordinarily, improvement or apparent cure is evident in 5 or 6 days. If a given patient is then unimproved, the use of a different drug is indicated. The fact that a patient has been treated with sulfanilamide and not cured, only slightly decreases her chance of cure with sulfapyridine. Many such cases have been successfully treated. Rarely, patients may not appear cured until 2 or 3 weeks after treatment is completed.

The high standard for evidence of cure suggested by the American Neisserian Society requires that

- 1 Spreads and cultures taken at 2 week intervals shall remain consecutively negative for 4 months
- 2 The cervix must appear normal
- 3 Leukorrhoea must be cured, or at the most, should amount to no more than a small amount of clear mucus

For obvious reasons, the exact fulfilment of all these requirements is difficult or impossible to carry out faithfully in any large number of consecutive cases. For purposes of scientific accuracy, I shall use the term "apparent cures" in quoting statistics hereafter. In the different studies to be mentioned, careful reexaminations of patients have been combined with many repeated laboratory studies of spreads and cultures.

APPARENT CURES—WITH SULFAPYRIDINE

- 1 E. D. Barringer, Horowitz and Strauss, 100 cases. Apparent cures—67 per cent. Dosage—5 grams for 3 days, 3 grams for 4 days.
- 2 J. F. Mahoney and Van Slyke have more than 80 per cent of apparent cures in women, using a dose of 3 grams for 1 day and 2 grams of sulfapyridine on subsequent 7 days.
- 3 In the New York City House of Detention—Nimelmann in consultation with Mahoney and Van Slyke has treated 650 women.

with gonococcal infections Two grams of sulfapyridine were given daily for 8 days About 80 per cent of these cases are in the "apparently cured" group *

There can be no doubt of the great efficacy of sulfapyridine in the treatment of gonococcal infections

SULFATHIAZOLE

During the past year, numerous reports of the extraordinary results achieved in the treatment of pneumonia with sulfathiazole have appeared in the literature The results here have been so spectacular that prior to the very recent appearance of the drug on the market, but little was obtainable for investigative work in gonococcal infections * Consequently, I can only report the results of a limited number of cases treated under the supervision of J F Mahoney of Staten Island, Fred Adair of Chicago, and myself

In New Haven, over fifty patients with gonococcal infection have been treated with sulfathiazole during the past 4 months by myself and my associates Thirty of these were women A standard dosage of 2 grams per day (i e, 0.5 gram given at 8 00 a m, 12 00 m, 4 00 p m and 8 00 p m) has been given every patient for 12 days and no longer All of us have noted that fewer patients complained of toxic symptoms than is the case when sulfapyridine is prescribed Transitory malaise, mild headaches, or anorexia have been common, but in no case have severe, toxic symptoms necessitated suspending treatment We have seen no urinary disturbance or blood dyscrasias In the majority of patients it has not been possible to have routine blood counts and there have been no reactions performed

critical blood counts Since we have only been using sulfathiazole for 4 months, I can

Using large "apparent" results, although patients who appear cured after 4 days after sulfonamide treatment commonly remain cured to stop treatment women treated showed marked clinical improvement in 100 patients so that at the most after treatment was begun All of them

In our own investigative spreads or cultures Two patients did not respond to sulfapyridine per courses of treatment and had to be re-treated Two as sleepiness, faintness, no cure, showed spermatozoa in the spreads taken One private patient had admitted intercourse with infected partners and was under observation She told us of results in 1745 cases of gonococcal infections treated with sulfa-

different authors see the report by Van Slyke Wolcott and Mahoney *
Lubbe & Sons the author has been supplied with sulfathiazole for the
months since June 1940

both developed what we may fairly call re-infections. One patient with acute salpingitis was rapidly cured of her tubal disease, but some weeks later developed a Bartholinitis. In the remainder of our patients, discharges rapidly disappeared and spreads and cultures remain negative. It is reasonable to believe that 90 per cent or more of the group are cured. Obviously one must keep patients from having intercourse with infected partners, or anyone else if possible. This is far easier said than done!

Adair⁶ reports that in his clinic seventy-one women have been treated for gonococcal infections with sulfathiazole. Fifty-five of them were followed and of these forty-five appear to be cured. Five at least and possibly ten of his patients appear to have contracted re-infections while under observation.

Mahoney⁷ has treated 125 patients with gonococcal infections with sulfathiazole—105 men and 20 women. None of his patients suffered from toxic symptoms sufficient to keep them from the activities of every day life. It is interesting that in the male group 91.1 per cent were cured. All twenty women in Mahoney's series rapidly yielded negative spreads and cultures. All showed evidence of clinical cure. He estimates the rate of cure in this group as 90 per cent or better.⁸

Sulfathiazole is less toxic than sulfapyridine and is consequently more easily administered. The high rate of apparent cures in the relatively small number of cases reported suggests that it is apt to supplant sulfapyridine in the treatment of gonococcal infections.

SALPINGITIS

In dealing with gonococcal infection, one must always remember that its normal habitat is found in and under the mucosa. This is true in tubal as well as in cervical infections. Pyosalpinx or hydrosalpinx not infrequently follows an attack of gonorrheal salpingitis. Formerly the tubal contents were deemed sterile in these cases. More recently, Studdiford and others have shown that gonococci may be cultured from pus tubes removed long after the initial attack.

A correct diagnosis of acute gonococcal salpingitis is usually made without great difficulty. The history and the fact that it is almost invariably bilateral and usually accompanied by an obvious cervicitis, ordinarily make it a simple matter to come to a correct conclusion. We have all learned that operative interference is dangerous and unwise.

until acute symptoms have subsided. A modified Fowler's position, hot douches, ice bags with fluids and supportive treatment used to be our mainstays. If a pelvic abscess developed, its evacuation and drainage through the vaginal vault was indicated, as it is today. Subacute or chronic salpingitis was treated with non-specific protein therapy, which was later discarded as unsatisfactory. The development of diathermy enabled us to introduce heat into the pelvic structures and proved of real value. Many patients were relieved of pain more adequately than could be done even with opiates. There is also good evidence that inflammation subsided, pelvic masses diminished and resolution took place more rapidly than under any other then-known form of treatment. If a patient had suffered with former attacks of salpingitis, operation was, and is still, often indicated a week or more after the temperature returns to normal. Ordinarily under such circumstances a supravaginal hysterectomy combined with a bilateral removal of the tubes is indicated, if it is judged wise to operate at all. The ovaries should not be removed if their condition warrants leaving them in situ. In judging whether to operate or not, one must consider the age of the patient, her past history, her situation with regard to children, as well as her symptoms, unless the amount of pelvic pathology dictates the decision. It must be remembered that while an attack of gonococcal salpingitis often or even usually renders a woman sterile, such is by no means always the case. I have seen one patient who became pregnant 6 months after I had myself drained a large pelvic abscess which resulted from a gonococcal infection of the tubes. When operating, one is often tempted to try conservatism by sparing one tube which may appear less affected than its mate. Doing so, or performing partial resections of tubes is nearly always a mistake. We have all had occasion to regret overconservatism and have rarely regretted the performance of a complete removal of both tubes when it was indicated.

If both ovaries are removed of necessity, the patient—usually a young woman—may later suffer severely with symptoms of an artificial menopause. In these circumstances, headaches, vertigo and vasomotor symptoms can often be made tolerable by the administration of estrogens. Stilbestrol given orally in doses of 1 to 5 milligrams per day often gives extraordinary relief. If this produces toxic symptoms, hypodermic administration of other estrogens may be necessary. Luminal given by itself may serve our purposes.

USE OF SULFAPYRIDINE AND SULFATHIAZOLE IN GONOCOCCAL SALPINGITIS

Sulfapyridine and sulfathiazole are rapidly revolutionizing the treatment of all forms of gonococcal infections. Their exact modus operandi is not clearly understood, but is supposed to depend partly on their ability to stimulate an immune reaction and partly on an ill-defined inherent action as an antiseptic. Cases of acute and subacute salpingitis respond to treatment with these drugs in what is often a dramatic manner. The amount and method of giving them is the same as that just recommended for gonococcal endocervicitis. Our own experience with the use of sulfathiazole includes only six cases classified as acute or subacute. In 2 to 3 days, and at times much sooner, after treatment was initiated, pain and fever nearly or quite disappeared. The relief of pain is apt to be commented upon by the patient within 12 or 24 hours of the institution of therapy. So striking is the improvement that diathermy or opiates need not be used. The tense abdomen quickly relaxes and the patient becomes comfortable often before one would believe such a thing possible.

As the patient improves, the mass felt on bimanual examination diminishes and becomes less tender. In one of my own patients, who admitted hospitalization for previous attacks, the masses diminished but did not entirely disappear, although symptomatic relief was complete.

Van Slyke removed the tube soon after an acute attack from a patient whom he had treated with sulfapyridine for acute salpingitis. The normal appearance of the tube was noteworthy. In another case in which I was interested, an inspection of the pelvis was made during an appendectomy three weeks after treatment with sulfathiazole for acute salpingitis. While the tubes themselves appeared normal, adhesions at their distal ends evidenced the accuracy of the earlier diagnosis. Evidently our decisions as to when and when not to perform salpingectomies will be modified in favor of greater conservatism as we gain experience in using chemotherapy.

It is evident that old residual pathology, such as adhesions and malpositions which cause pain, must be dealt with surgically as formerly.

GONOCOCCAL VAGINITIS OF CHILDREN

Alfred Cohn and his associates, with whom I have been connected, recently reported the results of their long study of this troublesome

disease In a large group of untreated children about 75 per cent recovered in 6 months or less Vaginal suppositories of estrogens, which have been widely used, were found to give apparently good clinical results with smears which early became negative That these results are more apparent than real is shown by the fact that cultures taken from the infected children so treated remained positive about as long, and as often, as in the untreated controls Sulfapyridine given at 4 hour intervals four times per day cured about 90 per cent of a series of cases in which it was given The dose for a child should not exceed 0.03 gram per pound of body weight daily, and should not total more than 2 grams per day

As the newer drugs that we have discussed come into wider use, we may confidently expect a striking decline in the incidence of gonococcal infections throughout the country

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

OCTOBER 3—*The New York Academy of Medicine* Executive Session—*a*] Reading of the minutes ¶ Papers of the evening — Arterial Hypertension — *a*] Medical aspects, Edgar Allen, Consultant and Chief of a Section in the Division of Medicine, Mayo Clinic, *b*] Surgical aspects, Loyal Davis, Professor and Chairman, Division of Surgery, Northwestern University ¶ Report on Election of Fellows

OCTOBER 31—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The First Harvey Lecture, "Studies on Lymphocytic Choriomeningitis and Poliomyelitis," Charles Armstrong, Surgeon, U. S. Public Health Service, National Institute of Health

SECTION MEETINGS

OCTOBER 1—*Section of Dermatology and Syphilology* Presentations of Cases ¶ General Discussion ¶ Executive Session

OCTOBER 4—*Section of Surgery* Reading of the minutes ¶ Presentation of cases—*a*] An unusual case of multiple fractures and dislocations, D. Rees Jensen ¶ Discussion, Herbert M. Bergamini, *b*] Case illustrating combined traction-compression method for treatment of bicondylar fracture of the tibia, Robert A. Wise ¶ Discussion, Condict W. Cutler, Jr., *c*] Cases of fractures by muscular violence produced by convulsions after metrazol therapy for schizophrenia, Louis Carp ¶ Discussion, Russell E. Blaisdell ¶ Papers of the evening—*a*] Metacarpal-phalangeal dislocations, William Darrach, *b*] Convalescent care of the fracture patient, Robert H. Kennedy ¶ General Discussion ¶ Executive Session

OCTOBER 8—*Section of Neurology and Psychiatry* Presentation of case—A case of Klippel-Feil syndrome with asym-

bolia, Frances Cottingham (by invitation) ¶ Discussion, Richard Brickner ¶ Papers of the evening—*a*] Erroneous recognition (*fausse reconnaissance*), Clarence P. Oberndorf ¶ Discussion, Nolan D. C. Lewis, *b*] Some observations on Menieres syndrome and its relation to migraine and epilepsy, Miles Atkinson ¶ Discussion, Harold G. Wolff, *c*] Electric shock therapy in mental disorders, S. Eugene Barrera (by invitation), I. Kalinowsky (by invitation), William A. Horowitz (by invitation) ¶ Discussion, Clarence O. Cheney, Karl M. Bowman

OCTOBER 10—*Section of Pediatrics* Program presented by members of the Mount Sinai Hospital Staff ¶ Reading of the minutes ¶ Papers of the evening—Symposium on suppurative and necrosuppurative bronchopneumonia in children —*a*] Pathogenesis and pathology, Alexander Thomas (by invitation), *b*] Clinical manifestations and complications, Herman Hennell, *c*] Roentgen features, Coleman B. Rabin, *d*] Treatment, George J. Ginandes (by invitation), *e*] Aerobic pulmonary abscess, Arthur S. W. Louroff, *f*] Pleural complications, Harold Neuhoof ¶ General discussion

The Sections of Ophthalmology, Medicine, Genito-Urinary Surgery, Otolaryngology, Orthopedic Surgery and Obstetrics and Gynecology held no meetings in October because of conflict in dates with the Graduate Fortnight

AFFILIATED SOCIETIES

OCTOBER 4—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) The Middleton Goldsmith Lecture was delivered by Dr. William Cramer on The Sex Hormones and the Endocrine Balance

New York Roentgen Society Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October

DEATHS OF FELLOWS

CAMAC, CHARLES NICOLL BANCHER 2703 Highland Avenue, Altadena, California born in Philadelphia, Pennsylvania, August 6, 1868, died in California, September 27, 1940, received the degree of Bachelor of Arts from the University of Pennsylvania in 1892 and graduated in medicine from that institution in 1895, elected a Fellow of the Academy December 15, 1898 and served as a member of the Committee on Library from January 1909 to January 1914

Dr Camac was instructor of physiology at the University of Pennsylvania in 1895, at Cornell University Medical College he was director of the laboratory of clinical pathology 1899-1905, instructor of physical diagnosis, chief of the medical clinic, and lecturer in medicine 1905-1909, and professor of clinical medicine 1909-1910, and at the College of Physicians and Surgeons, Columbia University, he was assistant professor of clinical medicine from 1910 until his retirement. He was emeritus professor of medicine at the New York Polyclinic Hospital and Medical School and at one time was consulting physician to the New York City Hospital, and medical director and consulting physician to the Gouverneur and Bellevue Hospitals. He was a member of the Association of American Physicians, the Philadelphia Academy of Natural Sciences and the American Association for the Advancement of Science.

During the World War, Dr Camac served as a medical officer in the United States Army reaching the grade of Lieutenant Colonel.

Dr Camac was the author of a number of articles and books on the history of medicine, surgery and allied sciences.

COURTEN, HENRY CARLTON 94-27 118 Street, Richmond Hill, New York, born in Palmyra, New York, May 3, 1879, died in Richmond Hill, October 15, 1940 received the degrees of A.B. and A.M. from Yale

University, graduated in medicine from New York University and Bellevue Medical College in 1909, elected a Fellow of the Academy April 6, 1922.

Dr Courten was director of orthopedics at the Jamaica Hospital, attending orthopedist to the Mary Immaculate and Lutheran Hospitals, consulting orthopedist to the Flushing, Rockaway Beach and Evangelical Deaconess Hospitals, and director of orthopedic surgery at the Queens General Hospital. He was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the Queensboro Surgical Society and the County and State Medical Societies.

HEAD, SIR HENRY Hartley Court, England, born in London, August 4, 1861, died in Reading, October 9, 1940, attended the University of Halle, Germany, the German University of Prague, Czechoslovakia, and Trinity College, graduated in medicine from the University of Cambridge in 1892, elected an Honorary Fellow of the Academy November 18, 1926.

Sir Henry became a member of the Royal College of Surgeons in 1890 and a member of the Royal College of Physicians in 1894. Since 1900 he had been a fellow of the Royal College of Physicians.

As early as 1889 Sir Henry, working in Herings laboratory in Prague, began his fundamental reports on the functions of the peripheral nerves. His investigations on the cutaneous distribution of pain and tenderness in visceral disease showing that the segmentation of the cutaneous areas affected by the different viscera corresponds with that belonging to the root ganglions of the spinal nerves are known to every medical student. These areas are now known as "Head's zones." In 1903 he made the unique experiment of dividing his own left radial and external cutaneous nerves. The observations of the loss and restoration of sensation which he experienced, together with extensive subsequent investigations, led to a new classification of sensory paths.

Sir Henry was at one time the editor of the medical publication "Brain," and the author of many medical papers and several volumes on neurology.

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IN THEIR CONTRIBUTIONS

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HUMANISM AND SCIENCE*

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The Linsly R Williams Memorial Lecture

I AM VENTURING to link Humanism with Science it is my purpose to direct your attention to an attitude of mind which I hold to be so characteristic, so strongly reminiscent of Linsly Williams that the whole theme of my talk tonight is intended as a tribute to that lovable man

It is a perilous honor to speak of him to this audience, but happily I can offer in this first Linsly Williams Lecture not merely the initial paragraphs, but the entire substance of the lecture in his memory I shall devote all of my efforts this evening to presenting a point of view which a scientist—especially a medical scientist might well adopt—a point of view which is rare in mankind and none too common among physicians, so far from common, indeed, that you will detect a certain nostalgic yearning in these remarks, an optative mood, an irrepressible desire that we might see more of it or at least hear more of it among physicians This point of view, this philosophy, was the frame of refer-

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ence for one of Linsly Williams' most precious traits I refer to his rare talent for combining sympathetically and therefore more effectively with a great many different kinds of people for his and their own good and the good of all of us. If you knew him no illustrations are needed to show how endearing can be this talent, and if I were to enumerate the benefits he brought to this Academy of Medicine, to the standards of our profession in this City, to the Public Health of New York, to the accomplishments and status of the National Tuberculosis Association, I should prove that this talent is important. And yet, to describe it as endearing and important does not suffice. The capacity to combine sympathetically with a wide variety of persons is one of many metals lying embedded in the matrix that I attempt to indicate by my title—Humanism and Science.

I offer no apology for reaching into the past and into fields far removed apparently from modern science in order at the outset to place before you what I mean by the word "Humanism." Whenever permitted by circumstances to enjoy the luxury of reflection, man has been drawn repeatedly to thoughts about three types of relationship: his relation to God, his relation to himself and his fellows, and his relation to the world of nature. I have not time for many examples of this triad of civilized preoccupations. Suffice it to note that in Europe by the late Thirteenth Century man's relation to God had become a preoccupation so elaborated and so dominating as to minimize, if not indeed to exclude, reflection upon man's relation to man and to the natural world. Intuitive curiosities had already been trimmed down into dogmatic utterances, spontaneous interest had been pruned into orthodoxy. The spiritual and intellectual outlook of man was firm—in fact it was rigid. Authority, not evidence, was the final arbiter, the term for disagreement was heresy. So powerful had the theologians become that even reflection upon the phenomena of nature invited attack and perhaps persecution. But such stagnation of the mind and spirit did not endure forever. Beginning in Italy, not in the great university of Bologna but in several places and cumulatively, there came in the Fourteenth and Fifteenth Centuries a revolt against the theologians and the scholastics. Now no one ever writes histories from the losers' point of view—especially when the losers have long been the authoritative element. And so it never becomes part of the tradition or the talents of those in authority to learn the earmarks by which to distinguish a powerful movement from mere sound and

fury, a dangerous maelstrom from concentric froth And thus this growing movement in Italy flourished on the underestimation of the authorities

Probably the growing leisure and wealth of the Italian city-states gave greatly increased margin for contemplation, for cultivation of the mind and of the spirit Petrarch wanted Chrysolaras from Constantinople to teach Greek in Florence in 1396 Undoubtedly the fall of Constantinople fifty years later and the resultant deposed Byzantine scholars coming as emigrés to the West made available the enormous wealth of Greek and Roman classics and provided material for the eager young scholars to study and to imitate In any event a tremendous force was set in motion The Humanism of the Middle Ages was born—and man was reestablished as the delightful object of fresh free contemplation, not the mere victim of theological orthodoxy and its allied political despotism This kind of attention to man was fresh and free, even if one cannot claim that in the full sense it was new, since the classical authors had been similarly interested in human nature The Italian humanists used the word *humanitas* to mean *culture* and happily quoted Protagoras the Sophist's "Homo Mensura" "man is the measure of all things" I said that Humanism was born but if one recalls the literature of antiquity it is more appropriate to say that the humanist attitude was revived Mankind has always been stirred more by resurrection than by birth, and Humanism was an enthralling resurrection In it reverence for the residual wisdom of the ancients blended with astonished delight at the rediscovery here and now of human values To use a current metaphor, a new yardstick was at hand—*homo mensura* It was something like finding that your great-grandfather's watch keeps perfect time The classical authors were found to be wise, witty, apposite, liberal, mellow, delectable—and all this in overwhelming contrast to the arbitrary dreariness of the theologians

No wonder that such a delightful release of the spirit of man from exclusive theological preoccupations invited literary composition in the vernacular The "here-and-now" received an intoxicating fillip from antiquity, from the classics which portrayed so graciously and so elegantly the enduring identity of human nature Freedom comes so frequently from a recognition of limitations, and humanism through its mellow recognition of sameness in variety, produced and still produces fuller consciousness and freer faculties What random heirlooms we

receive from the past' The degree of LHD at Oxford crowns the curriculum of *Litterae Humaniores* And Sir Walter Fletcher used to insist that our American usage of the word "Humanities" is historically unjustified since "the Humanities" comprised all those studies which were not "the Divinities" Therefore, he said, his favorite, Physiology, manifestly should rank as one of the humanities'

I trust this historical excursion does not deserve Lord Balfour's comment on a certain type of exposition of "what we understood much better before it was explained" Before proceeding further it may be well to reiterate that among the three eternal subjects of human speculation and curiosity—God, Man and Nature—Humanism has been an affirmation of the importance of Man and his values Like other "isms," Humanism has presented its affirmations with some of the flavor of protest and revolt And like other "isms," Humanism has been misrepresented by some of its adherents and misconstrued by many of its opponents

The humanist is not a worshipper of the past If he be retrospective it is to round out his perspective His delighted and accurate familiarity with the Classics—whether Latin, Greek, Sanskrit or Chinese—is comparable to the satisfaction an experimental physiologist takes in the crucial and elegant experiments of Harvey or the wise nod of the clinician in reading the Hippocratic Oath The humanist is not interested in the past merely because it is past As the statistician likes a long series, not a short one, the humanist similarly likes the long accumulations from the past to illustrate the nature of man No worshipper of the past, he is, however, far from being a modernist Indeed the humanist would prefer to be taken for almost anything but a modernist His particular aversion to modernism is perhaps due to his dislike of the pride that characterizes belief in all that is modern In this point I side with the humanists Indeed I would fain devote some effort to lay bare the nature and the full measure of our contemporary pride—so uniform and so unchallenged is it Ours is the pride of the cheering section not of the lonely defiant individual We are proud in a manner almost unknown to the past The hubris of the Greek tragedy was typically the overweening pride of the individual we scarcely comprehend the fascination for the ancients of this kind of tragedy, for our characteristic pride is of a different sort, we glory in an ineffable certainty that being modern, and all of us being modern together, we

are therefore insuperable. Our madness is not the pride of Goliath but of the Gadarene herd. In numbers, in numbers reassuring each other by deriding the past, we invite the disaster promised to the chief of the Seven Deadly Sins. To insist that the present is pregnant with perfection is a sort of provincialism not in space but in time. Indeed why say provincialism when there is still a better word—parochialism!

In contrast with the parochial satisfaction in all that is modern, the humanist insists upon the invariability of human nature despite changing creeds and customs. "*Plus ça change, plus ça reste*." The humanist has this in common with the scientist—he is interested in those uniformities which repeat and reappear inescapably in the manifold of experience. The humanist interests himself in values which may advance without changing, the dogmatist, whether in science, religion, or politics, is too often concerned with things which change without advancing.

Though he who insists upon the sameness of human values may find the past and its classic literature peculiarly appropriate to his theme, the true humanist does not exploit the Classics. He does not feign authority, respectability or dignity by quoting Latin or Greek, or with careless inaccuracy appropriate from classical tradition. I wish I could say as much for the members of our own profession. Permit me one example of the spurious dignity and ignorant pretension the humanist disdains. The symbol of Aesculapius, the God of Healing, is a staff with one snake twisting around it. The symbol of Mercury, the God of Gaming, Commerce, and Communications, is the Caduceus, a staff with two snakes symmetrically entwined. The United States Public Health Service, the University of Chicago Press, the Medical Corps of the United States Army, innumerable hospitals and not a few medical societies hold doggedly to the decorative but rather misleading emblem of the patron of taking chances, taking profit and carrying tidings elsewhere. Granted that mercury is not without therapeutic indications, nonetheless architects and engravers, Trustees and Congressmen should be implored to confine the use of the Caduceus to the adornment of the Stock Exchanges, the Chambers of Commerce and Post Offices and be cured of seeing two snakes where one would better indicate the sober dignity of the Aesculapian tradition.

Now let us proceed to another confusion rather more subtle and more common. Humanism is not Humanitarianism. To confuse Humanism with Humanitarianism gives to the humanists a distress apparently

as acute and impassioned as we afford Socialists in confusing them with Communists. And perhaps rightly, for if words are the coinage of thought, no one will feel happy at being shortchanged. Both humanist and humanitarian reject a too exclusive preoccupation with God: the humanist because he is categorically opposed to too much of anything, the humanitarian because he feels the service of man to be the more cogent part of the First and Great Commandment. The humanitarian seems to substitute the service of man for the worship of God, the humanist wants balance and proportion between man's preoccupations with God and all man's other interests. The humanitarians would hold the humanists to be heartless intellectuals, contemplative and cultivated but not unselfish enough. The humanist, on the other hand, might find humanitarians offensive when they are over-zealous, Irving Babbitt's rapier flashes in this allusion to the humanitarians: "If it can be shown that there has been no vital omission in the passage from the Service of God to the service of man one may feel safe with all the altruists, from the third Earl of Shaftesbury to John Dewey."*

Again Humanism is not mysticism. It is in clear distinction from mysticism. Humanism appreciates rather than opposes religion. G. R. Elliott notes, "Theism at its worst fosters as nothing else can the proud imaginations of the human heart. Humanism, which in one of its most important functions is a criticism of religion, is essential for sound religious humility."** One wonders whether it is not essential for sound humility among scientists too. Humanism calmly declines to join in fanatic sorties of credulity or absolute surrenders of judgment. On the other hand the humanist is no advocate of immobility and repression. He is the partisan of give and take, of suppleness of adaptation, of easy sorties and sure returns, of the delicacy inherent in well-modulated strength, as R. B. Perry says, "of whatever influences conduce to freedom." It is quite natural that Osler, the humanist, took *Aequanimitas* as an object of his delighted attention.

Humanism possesses a quality curiously like the homeostasis of the organism, from any excursion too far out into the extremes of dogma or spiritual despotism it returns with persistent decorum to the nature of man as the center of operations and term of reference. The decorum of the organism is called homeostasis. Humanism stands for a similar

* Irving Babbitt "Humanism—An Essay at Definition" *Humanism and America* p. 30 edited by Norman Foerster, Farrar and Rinehart, New York, 1930.

** G. R. Elliott, 'The Pride of Modernity' *ibid.* p. 98.

decorum of the judgments and enthusiasms of the mind "*Homo mensura*"

Let me quote from Irving Babbitt in Norman Foerster's "Humanism and America "

"As is well known, the word humanist was applied, first in the Italy of the Fifteenth Century and later in other European countries to the type of scholar who was not only proficient in Greek and Latin but who at the same time inclined to prefer the humanity of the great classical writers to what seemed to him the excess of divinity in the mediaevals. This contrast between humanity and divinity was often conceived very superficially. However, the best of the humanists were not content with opposing a somewhat external invitation of the Ciceronian or Virgillian elegance to the scholastic carelessness of form. They actually caught a glimpse of the fine proportionateness of the ancients at their best. They were thus encouraged to aim at a harmonious development of their faculties in this world rather than at another world felicity. Each faculty they held should be cultivated in due measure without one-sidedness or over-emphasis whether that of the ascetic or that of the specialist. 'Nothing too much' is indeed the central maxim of all genuine humanists ancient and modern.

"In a world of ever-shifting circumstance, this maxim is not always of easy application. Whoever has succeeded in bridging the gap between the general precept and some particular emergency has to that extent achieved the fitting and the decorous. Decorum is simply the law of measure in its more concrete aspects. For every type of humanist decorum is in Milton's phrase, the 'grand masterpiece to observe' ".*

Does the role of the humanist begin to be clear? In the avoidance of extremes he warns and protects against the preoccupations of the theologian and of the specialist.

With the history and attributes of Humanism in mind we can now define more explicitly what valid relationship can obtain between Humanism and Science. I may as well say immediately that I think scientists are badly in need of Humanism. Bounden specialists that we are, if we are not to become lost in a fog of our atomized subdivisions of knowledge we must heed the humanist when he says to any one of us, "All

* *Op Cit* p 26

that you say may be true but I must weigh its *value*, for I am a man and man has certain limitations and certain undetermined faculties, and long experience shows it is inane for him to be governed by frenzied conviction or fanatic obedience." It is scarcely a coincidence that the land of *fachmanner*—specialists—is become the land of frenzied conviction and fanatic obedience. As Humanism once provided the corrective to a too exclusive preoccupation with divinity, it will be wise ere long to look to Humanism for a corrective to man's too exclusive preoccupation with nature. The limitations of natural science are far more real than apparent, and far more important than we scientific moderns suppose. The limitations of a too exclusive preoccupation with science come down to this. Science offers neither meanings nor values. That is the defect of its quality. Nothing is to be gained by complaining that science offers man no system of values. It doesn't pretend to. We must look elsewhere for interpretations and meanings. Not even in the pronouncements of most psychologists are there as many abiding values for human beings as in great literature. And even if psychologists were to come upon what man needs, so pitiful is their ignorance of the art of expression that their findings would remain untranslated for a generation.

Just as the material of different sciences shapes the language and determines the type of thought proper to each science, so the permanent concern of the humanist with what conduces to man's freedom, to fuller consciousness, and a more graceful balance in living, produces a special power, a sort of style of mind and spirit. In such a style the connoisseur and the amateur join hands—a style appropriate to understanding and enjoying all of being human, not just to the elucidation of some part or function of being merely alive. The humanist, using the accumulated experience of human beings in their variegated business of being human, prepares himself to answer that devastating question, "What of it?" And in preparing us to reply to that question the humanist virtually says, "In your capacity as a human being you cannot afford to ignore the residual wisdom of the best of human beings. You must learn what they knew of the limitations and the freedoms appropriate to man." We hear a great deal nowadays among psychiatrists of the "total situation," "the total personality," "the cultural matrix," "the life situation." These crude groping phrases, these homeless neologisms seem like the outcries of a disoriented specialist in search of a set of values, values not merely for the America of 1919.

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at any time. The most painful limitation of psychologists is their provincialism in time. Their field has been tilled in their manner not a hundred years, but apparently they will not bother with what was true before they came. More than most scientists, because they set out to study the psyche, they need to correct the absurdities and excesses of their specialism with the perspective of the humanist.

Let me repeat, Science offers us no system of values, no canons of good taste. Science is interested in what has logic, order, system and often in what has use. The humanist on the other hand, though not indifferent to logic, system, and order or usefulness, predominantly interests himself in what has value—in what long experience has shown to be the delights and satisfactions proper to mankind. There is a charming word—perhaps it is scientific slang to justify the right we have to our predilections, to our hobbies, to our enthusiasms be they never so irrational. The word is *ich-gerecht*. No humanist but would instantly wink with understanding at *ich-gerecht*—and waive all defensive explanations.

Humanism concerns itself with what has value, not what has use. Hans Zinsser, whose brilliant vitality illumined even the shadow of his death, expressed a restless dissatisfaction with the limitation of Science. Writing of course, of himself, he says

He became, however, a profound admirer of Whitehead, who, it seemed to him, combined—in the wide horizon of his mature wisdom—deep erudition of the sciences with sensitiveness to aesthetic values, appearing in this regard to possess some of the qualities, less creative but perhaps more contemporaneously sound, of a Goethe. It was in Whitehead's diagnosis of the sick world that R S recognized his own, less learnedly arrived at, to the effect that, with the rapid development of industrialism and urbanization (both consequences of the scientific control of natural forces) there was a neglect of the "aesthetic qualities of the new material environment," there was a limitation of the "moral outlook" at a time when it was most needed. The "moral pace of progress," says Whitehead, "requires a greater force of direction," but a grooved professionalism (also a consequence of the headlong rush of science) has brought it about that "the leading intellects lack balance" and "the task of coordination is left to those who lack either the force or the character to succeed in some definite career." The corrective, therefore, it seemed to R S, should lie not in the checking of science, but

rather in catching up with it

Thus, with Whitehead's assistance, R S thought he understood the general diagnosis. But that is as far as he got before he died. He stood before the problem as he often stood at the bedside of a dangerously sick patient, helplessly hoping for greater physicians to point a way of cure. He looked to art, literature, and criticism as the instruments through which this might come. For it seemed to him that what had happened was that mankind had been so busy planting the potatoes and corn and turnips of life that it had forgotten to tend the gardens. And now it had no gardens in the enjoyment of which it could find the reasons for which it had planted the potatoes and the turnips. For the arts and the spiritual values which they represent (and this was the pathology of the disease) had come to be regarded as trivial and not worthy of the efforts of serious men, a speculative commodity like stocks or postage stamps for rich collectors or a plaything for amateurs and eccentric incompetents, at best, a civilized amusement or a hobby.*

Where the humanist of the Fifteenth Century felt his natural interests restricted by the confines of theological dogma, the humanist of the Twentieth Century finds his interests and his aesthetic needs neglected by science. But the position of the Twentieth Century scientist is worse still. Can he derive a sense of meaning and significant direction from the one-sidedness of specialism? He may have a modernist's pride in the few trees he knows and their modern growth but what is to give him a sense of the forest, of the extent, the meaning or the beauty of the forest? Without some canons of taste and standards of loyalty to hold and cultivate in common with others, the true scientist feels—as some have confessed to me—a disquieting suspicion that his life taken as a whole is lacking in significance. There is something missing. Ah, there comes in the idea of value! Our scientific, modern, objective, practical view fails to note the age-old nature of man which if it is modern is also ancient—age-old but timeless. Would we moderns not find in Humanism and the humanistic attitude the most stimulating as well as the most congenial climate in which to develop our systems of values and meanings—most stimulating because of the length, breadth and catholicity of the humanistic tradition reaching as it does into remote antiquity, and most congenial because free from dogmatism and

* *As I Remember Him* by Hans Zinsser. Little, Brown and Company, 1940, pp. 422-423

mysticism—both of which, when recognized, are unwelcome to the scientist's mind

And if the scientist needs Humanism for himself, how much more is to be said of the scientifically trained physician upon whose store of faith, equanimity and sense of proportion and of value still others expect to depend? In the Gifford Lecture of 1914 Balfour* remarks that science "like common sense regards the things which are experienced as being themselves unaffected by experience." Let us grant that is true for most of the clinician's observation of death, of suffering, of disability or dysfunction! To witness death is not to affect it, to observe a disability is not to modify it. But the physician's task is not merely to observe, he must reason to a conclusion and proceed to treat. How long does the patient whom the physician is experiencing at the bedside remain "unaffected by the experience?" For a miraculous moment comes when the doctor becomes the treatment. And it is just there that science like a relay runner must pass the torch to Humanism. Science, the fruit of man's preoccupation with nature, must then give place to Humanism, the flower of man's experience with man. It is then that the riches of Humanism are needed, its wealth of corrective equanimity, its reflective philosophy of values, its insistence that the tastes of man may be of supreme importance to making his life worth living, and his death worth staving off.

Disease has many facets. Pain, disability, and death make up the most obvious among them. Over these three, pain, disability, and death, Science has won and will win yet more immeasurable victories. Let no doubt insinuate itself that the day of Science in medicine draws to a close. Quite the contrary—the application of biology, of physics and chemistry to disease is in the ascendant. But disease has other aspects—uncertainty, for example, or fear and shame and the distress at letting down one's fellow men. Indeed it is these human aspects of disease which are the hardest to bear, for which we physicians are most poorly prepared and in which scientific medicine has least to offer.

These are disturbances of a different order. They are not derangements within that neatly fitting boundary known as the human skin. More nearly they are disturbances within far wider boundaries, the patient's human relationships, his social protoplasm in which he feels himself, as it were, the nucleus, at once essential and dependent. We

* *Theism and Humanism*. The Gifford Lectures in 1914. p. 136. George H. Doran Company.

take it for widely known that disease distorts relationships of organs, tissues and functions within the body but only imaginative experience can convey an idea of the extent to which illness disturbs the relationship of the sick man to his personal matrix—to his family, his friends, his colleagues, and not least to his image of himself in this matrix, an arcanum, a secret inner chamber of his being, ineffably precious and delicate. Think, for example, of the domestic tyrant stricken with heart disease. He is totally unprepared for his sudden dependency upon his wife—of all people his wife whose married name had been Alice to tremble at his frown. And now she smiles at his helpless tantrums. It is not his shortness of breath, it is his tumble from omnipotence which infuriates and exhausts him. He cannot endure ceasing to dominate his colleagues, he cannot bear being pitied by his friends, ignored by his family.

Illness deranges us subjectively. It disturbs the values we have grown since infancy to attach to our status among other human beings. Can such derangements of our system of values be adjusted by science only, which admits it has naught to do with values and confines itself to experiences which are not modified by being experienced? The hasty answer would be certainly not. But that is wrong. Digitalis and rest in bed may reestablish the domestic tyrant in full possession of his faculties and prerogatives. But if science fails him—ah, then it would be wise to have a physician who is a humanist—like Linsly Williams. For such a physician knows how people are and how to handle them without mechanical recourse to specialism or the narrow logic of any one system of study. The restless imaginative curiosity, the marvellously accurate observations, the stern and flawless reasoning of the scientist are glorious. His humility in the face of his conclusions is ennobling, but he is always in danger of error. His is a special frailty. The commonest error of the scientist is to assume that he is master of all the variables in his equation. One more factor than he is aware of may be his undoing. And when the practitioner of medicine is only such a scientist, that elusive additional factor may be himself—his own unnoticed effect upon the patient.

The true physician cannot remain outside the manifold of the events he observes, and upon this simple fact one may rest the whole argument for the alliance of Medicine with Humanism.

For if we admit that the physician as a *person* enters into the relation of doctor-to-patient, it is uncomfortable to see how meagre is the

cultural baggage, how callow the manners, how unexercised the imaginations and sympathies of our medical students must remain unless we open to them the resources of Humanism for the enrichment of their training. If in the years devoted to medical and premedical education he has omitted all cultivation of tastes and all reflection upon ultimate values and the selection of canons of human behavior, how can the young physician possess a culture richer than the random residues of his youthful background? How can we expect such a one to have the spiritual valences that will enable him to combine effectively with patients in the bewilderment and loneliness and anxieties of illness? Hans Zinsser told me in 1923 that he was looking for an assistant "Only two qualifications are necessary—he must have read *Tristram Shandy* and be able to play the viola. I can teach him all the bacteriology he'll need to know!" If these were ever necessary for a bacteriologist what range of literature and artistic skill would be appropriate in a man fit to deal with persons as well as streptococci?

To the almost unlimited resources the humanists have made available in literature and the other arts a certain sort of physician remains conscientiously indifferent in the conviction that these records of the human spirit offer nothing of proper concern to the comprehension of man. I suppose that if the temptation to enjoy humanity through the humanities is not strong there need be no inordinate lament, but it seems sad that even timid pleasures are foresworn in the name of duty to patients. And the more so because some patients would rather be understood than be X-rayed, and rightly so.

Perhaps it is only because they are naturally imaginative, penetrating, quick in sympathies and broad in tolerance that some persons enjoy the great literature of Humanism. In that case humanistic tastes can be counted as the password by which we can recognize the radiant spirits in our profession. Or perhaps familiarity with *litterae humaniores* really nurses an infant sympathy and encourages a native tolerance so that imagination, sympathy and tolerance can be cultivated as well as merely recognized. In that event the study of great literature and the fine arts could serve as an invaluable supplement to medical science in the exercise as well as the preparation for the practice of medicine.

Before we leave the minor key of lamentation let us register regret that physicians repeat at times the paradoxical error of some scientists—the utterance of dogmatic finalities, in the presence, one might add, of

persons disposed to believe too readily. Such men behave as though today's science were definitive and final, yet all the while they devote their energies to its correction and modification. Science on the whole treats the manifold of experience as a causal series. The humanist treats it as a sequence of perceptions. The humanist then should supplement, not substitute, for the scientist, since the scientist runs the risk of failing to observe what he cannot explain in terms of cause and effect and the risk too of being dogmatic in his neglect of factors which do not lend themselves to his operations and form of study.

But on the whole physicians over the course of history give cause for robust rejoicing to the friends of Humanism. Until the Nineteenth Century they were not indentured in long service to the masters of natural science. Leonicens, Rabelais, Linacre, Champier, and Dolet and Canappe were physicians intimately effective in spreading the New Learning and put Mediaeval Humanism enough in debt to Medicine to justify future borrowings in the opposite direction. Fracastorius, who wrote the first description of syphilis, was a professor of philosophy who practiced medicine and wrote poetry. As August Krey observes,* "Pagolo, friend of Cosimo di Medici, professor of astrology and other forms of mathematics, practiced medicine for a few friends." Vesalius, Agricola, Paracelsus, Conrad Gesner—the list is brilliant and long. So brilliant that this new learning largely centering at Pavia, Padua and Pisa, the universities favored by Milan, Venice and Florence respectively, began to overshadow Bologna, Oxford and Paris, whose only hope was to join the humanistic movement. Close as was the association with the classics in the earlier years, the knowledge of Greek and Latin is not the essence of Humanism, though it was the earliest vehicle for that New Learning. Hippocrates and Galen, the scholarly tradition of the Renaissance, the nomenclature of anatomy, physiology, pathology and therapeutics, have at least anchored us physicians to the classical tongues. From time to time we may drag anchor a bit as, when an elderly gynecologist had the classical warning *Primum non nocere* painted upon the wall of the operating theatre, with a translation by a modern colleague which ran instead of "Above all do no harm"—*Primum non nocere*—"The first time doesn't make any difference." Dean Briggs of Harvard is said to have remarked that although the A B

* *The Meaning of the Humanities* Essay of August Krey on *History of the Humanities* p. 68 (Princeton University Press)

degree no longer assured a familiarity with Greek and Latin, the degree of B.S. was a guarantee of their ignorance

The essence, purpose and effect of Humanism in the Fourteenth and Fifteenth Centuries was to liberate the spirit of man from the despotism of theological and political orthodoxy by focussing attention upon man as the measure and frame of reference for all things. Humanism in any century has freed the faculties, widened the consciousness, reaffirmed the dignity and refreshed the gusty honesty of being human through clear-eyed acceptance of man's limitations and a happy insistence upon his potentialities.

It did more. With abounding grace, Humanism taught men to write again in the vernacular—a lesson sadly needed by medical writers of today. If we learned no more from the humanists than how to write English the linkage of Humanism and Science would be a godsend. With a public eager to understand more of science, the newspapers, despairing of the usual capacities of scientists to match the clearness of their understanding with the clarity of their expression, have begun to create a most valuable set of men called science writers. Since in democracies the support of research depends upon popular understanding of the nature of scientific work, scientists owe a great debt to these science writers. They have a delight in the use of clear, simple language and a realization of the potentialities of the here-and-now that reminds one of the mediaeval humanists, and like the humanists they have a feeling for the meaning and value of what they describe.

Meanwhile good writing in our professional journals is pitifully rare. Discriminating use of adverbs and adjectives is no mere literary embellishment. It is essential to the accurate and unambiguous recording of precise or complicated relationships. Where the order of events has meaning, excellence in narrative is no mere trick. James' *Chapter on Habit* and Osler's *Textbook of Medicine* are professional literature, it is true, but they transcend the usual boundaries of technical writing by virtue of their style. And who will deny Osler's freely acknowledged debt to the classical tradition of Humanism?

Somewhat as the science of statistics has developed a language to deal with series or classes of events in distinction to single events, so Humanism has developed a style of writing appropriate to express proportion and balance so necessary to the scientist who wishes to express his orderly comprehension, his power to put together again the frag-

ments he has obtained by analysis. Clear, vivid, enduring records of thought and feeling, of observation and inference come from a mind not too much enslaved to analysis or to seeing all phenomena in terms of causation. Even the act of observation may be disturbed by too much causal reasoning or too much familiarity with authoritative dicta. Wood Jones told me that for some twenty years the premedical students at the University of Adelaide had dissected the frog with the use of Huxley's manual. Now Huxley's manual was written for the dissection of *Rana temporaria*, the English frog. But the students were actually dissecting a frog anatomically different, *Rana australiensis*. In all that time only a scant dozen students had noted the differences between the frog they dissected and the frog in the textbook, and among the élite of those who noted that the frog was not just like the textbook not one student but concluded that his frog was *wrong*.

I trust this excursion into the need for better writing by scientists and perhaps especially by medical scientists will not seem unjustifiably remote from our consideration of the offerings of Humanism. For it is in his traditional economy and elegance of expression as well as his insistence upon balance and proportion that the humanist can serve as an ally if not a paragon. The scientist's lens to observe is bright: let not his mirror to reveal go unpolished!

I draw to a close. The limitation of science is that (quite honestly) it does not furnish us with tastes, significances, values, and meanings, though it provides us with an ever increasing diversity of what is interesting and useful. The attention of the humanist has for five hundred years and more been fixed upon tastes, values and meanings—the limitations and the freedoms of being human. Therefore, as may already be suspected, Humanism offers much to Science, especially in medicine where on occasion the physician will find a still imperfect science sadly inadequate to his patient's need. For in illness, fear, anxiety, shame, and uncertainty call for understanding, sympathy and imagination, courage and companionship, all among the Golden Treasury of Humanism. In the cultivation of these we must not rely merely on fortuitous circumstance. We physicians should resort to the treasure houses of literature and the arts, to the humanist and his familiarity with those values which are permanent for man.

As Humanism in the Fifteenth Century freed man from an extreme preoccupation with the exultations and the threats of the theologians,

it could serve now in the Twentieth Century to counterbalance the exultations and the threats of the specialists—whether they be mathematicians, physicists, biologists or psychologists. No, Humanism will still protest against exclusive preoccupations, against the limited horizon of dogma and finality. And therefore it deserves attention because it encourages independence, originality, honesty and a graceful proportionateness in understanding man.

I should feel gratified if during this hour you have been at times reminded of Linsly Williams. For in the best tradition of the humanist he had alertness to mankind, vitality of feeling, and a natural decorum. As a physician he had a clear-eyed but sympathetic recognition of the limitations of his patients and his friends and yet he knew how to encourage their potentialities and help them realize their hopes. He was a cultivated gentleman whose intellectual and esthetic tastes and beautifully balanced sympathies reached over a wide and delightful range. Far beyond most men he was a humanist capable of combining effectively with many kinds of persons to their advantage and delight, and to the welfare of us all.

TREATMENT OF BACTERIAL MENINGITIS*

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ANY logical treatment of bacterial meningitis must be approached from two fundamental angles, chemotherapeutic and immunological. Evidence for the importance of the role of inhibition by chemotherapy is entirely convincing. The part played by immune bodies, either passively induced by serum treatment, or following spontaneous production as a result of the active infection, has in general been overlooked due to the natural supplanting of older methods by new and simpler ones. During the period of rapid progress in chemotherapy there has been a corresponding advance in methods of antibody production due to the chemical approach, and accurate quantitative analysis of the amount present in a given serum, thus putting this type of therapy on a firmer quantitative basis.

In an effort to gain an objective approach we must first refer to experimental evidence on the status of these two mechanisms. Here individual varieties of meningitis must be considered separately, but before doing so it will simplify the discussion to list those under consideration: *Haemophilus influenzae*, *pneumococcus* and *meningococcus*. They will be discussed together as an immunological group for they possess a similar pattern of chemical components acting as antigens, inducing chemical reactions in the body. Without going into details, this similarity may be described by stating that each of the organisms of this immunological group is surrounded by a capsule containing a specific carbohydrate, and in the course of metabolism this specific substance is excreted into the surrounding medium. This point deserves emphasis here for it is on this evidence that a single general plan of treatment combining drug and antibody is advocated for all three forms of meningitis.

Since the *pneumococcus* has been the most thoroughly studied of this group, the experimental evidence will be drawn mostly from this

* Read October 17, 1940, in the Graduate Fortnight of The New York Academy of Medicine From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University, New York.

field It has been shown that the capsular substance is the important element of the organisms, upon which their specificity and power to invade the human body depend It is therefore logical that an effective therapy must be able to influence this mechanism Since these organisms excrete this substance into any surrounding substrate in which they are multiplying, it is understood that the free carbohydrate must first be neutralized before the same substance in the capsule of the organisms can be attacked The amount of free specific carbohydrate present in spinal fluid and blood of patients with pneumococcus meningitis is an index to the severity of the infection It is also an index to the amount of anti-carbohydrate antibody necessary for its neutralization and recovery from such an infection When the infection is of average severity and the biology of the organisms is interfered with and growth inhibited by chemotherapy, the natural antibody response takes care of this situation It has been shown that in pneumonia the rise in anti-carbohydrate antibody in the blood correlates with crisis, whether it is spontaneous or induced In drug treated patients and animals there is no evidence that antibody production is influenced in any way There is a correlation between recovery and antibody production just as in the spontaneous process The types of pneumonia which respond best to drug therapy also have the best antibody response Free antibody produced by the infection can be detected earlier in the course of the disease when the patient is treated with drug than during spontaneous recovery, because there is production of less antigen or specific carbohydrate which it must neutralize It would seem then that in recovery from pneumococcus infections, whether spontaneously, as the result of drug therapy, serum therapy, or a combination of these, antibody response is an essential part of the picture

This work has demonstrated how the amount of antibody essential for recovery may differ with the severity of the disease and why a quantitative approach is necessary You are all familiar with the great advance in immunological chemistry represented by an exact chemical method of quantitative analysis of the antibody in serum, whereby the amount of immune substance may be accurately determined and expressed in milligrams of immune nitrogen per cc Analysis by this method parallels analysis by mouse protection methods indicating that it is the anti-carbohydrate antibody which is the protective one This chemical determination eliminates the inaccuracies of the mouse protec-

tion tests After a given original dose, the adequacy may be tested by objective means, either by the Francis skin test, or by testing the patient's serum directly for presence of free anti-carbohydrate antibody It is only under such a regime that serum therapy can be evaluated either alone or in combination with drugs

The other outstanding advance in this branch of immunology which has clinical application is production of therapeutic rabbit sera and the demonstration of their superiority over horse sera

All evidence indicates that the biology of *H influenzae* and meningococcus is similar to that of the pneumococcus The parallelism is so great that there is every reason to assume that the role of the specific substance in the capsule is identical with that in the pneumococcus in influencing the severity of infection and in the formation of antibody spontaneously in patients and in production of antisera for passive immunization The direct evidence on this point, while limited, indicates that the anti-carbohydrate antibody is the protective antibody in both anti-meningococcus and anti-*H influenzae* serum The quantitative analysis methods originally developed for anti-pneumococcus rabbit serum have been applied with success to *H influenzae* rabbit serum by Michael Heidelberger The methods used originally by Squibb's for purifying and concentrating the globulin fraction of anti-pneumococcus rabbit serum have likewise been applicable to *H influenzae* antisera Evidence suggests that free antibody in the serum of patients treated with *H influenzae* antiserum is a valuable index to the adequacy of antibody for an individual instance Rough quantitative tests on the amount of specific capsular substance free in the spinal fluid of meningococcus meningitis patients are of definite prognostic value

First, I should like to discuss the treatment of meningitis due to *H influenzae*, for it is in this field that we have derived most of our clinical and laboratory experience which is responsible for the formulation of a general plan of therapy applicable to the other two varieties belonging to this immunological group, that is, pneumococcus and meningococcus The spontaneous mortality of *H influenzae* meningitis varies from 90 to 100 per cent, depending upon the age distribution of the group analyzed In patients less than 2 years of age the mortality approaches 100 per cent Our own experience, prior to the use of the treatment to be described, showed no recoveries in thirty-eight patients, twenty of whom had been treated with horse serum and complement

While the results of horse serum separately and in combination with drug therapy have altered the mortality significantly, the per cent of recoveries is still small. The best results reported in small groups showed a mortality of 67 per cent while large groups show a less favorable prognosis under the same therapy.

There have been a number of reports of single recoveries under drug therapy alone. One paper collected the results of eighteen cases treated with sulfapyridine alone with five recoveries, a mortality of 72 per cent. Only three of the recovered patients were under 6 years of age. In eighty-two patients treated by sulfanilamide, there was a mortality of 88 per cent. In thirty of these, serum was used in addition and four of these recovered. While experience shows there is more inaccurate bacteriology on this organism than any other, it is clear that recoveries do occur when drugs alone, both sulfanilamide and sulfapyridine, are used. This evidence supported by the demonstration of inhibition of this organism by all three drugs in common use, both *in vitro* and *in vivo*, warrants the use of drug therapy for its inhibiting effect. The selection of the best drug is difficult at the present time on the basis of objective evidence. Our own very limited results with all three drugs in mouse protection tests fail to show any significant difference. Verbal reports from one institution indicate superiority of sulfathiazole and from another that results of mouse protection tests with all the drugs were so discouraging that that form of therapy has been discontinued in influenza meningitis. Their clinical results at that time were in the same direction. Our own clinical experience fails to show a difference between sulfanilamide and sulfapyridine (sulfathiazole has been used in two patients, only one of whom recovered). Until the question of permeability of the meninges for sulfathiazole has been more thoroughly investigated, this drug should not be used in meningitis.

According to current views, antibody would seem to be an essential part of the recovery mechanism, whether it be manufactured by the patient as the result of the infection in the presence of drug therapy or whether antibody is introduced by serum therapy. In the present state of our knowledge derived from clinical experience and the advances in immunology, one must conclude that a combination of antibody and drug therapy should yield the best results in this disease.

Experience with the method to be described is still too limited to

be evaluated with accuracy. However, the results of its use in several institutions have been so encouraging that a detailed description seems warranted.

We have attempted to apply the fundamental principles discussed under recovery from pneumococcus infections to the therapy of influenza meningitis. The foundation which made possible the transfer of these principles was laid by Pittman. While there is no direct evidence on this point all evidence indicates that the ability of this organism to invade is linked closely to the production of free specific carbohydrate.

Our interest first centered around the production of rabbit serum in 1937, since our experience with horse serum alone had been very discouraging. All the knowledge of the biology and chemical structure of the pneumococcus has been utilized in the production of rabbit anti-influenza antibody. Heidelberger's quantitative chemical analysis of the amount of antibody produced under various circumstances with different types of vaccine has enabled us to increase the antibody tenfold over early lots and to put the dosage on a quantitative basis. The dosage of the first patients treated prior to the above work was based on volume of the serum tested by only relative methods, as was all serum therapy in the past. Sulfanilamide was the most thoroughly understood drug at the time and this was combined with the rather weak serum used on a volume basis. Since the first three consecutive patients treated by this method recovered and since subsequent experience showed the total amount of serum used on the first three to contain less than 100 milligrams of antibody nitrogen per patient, this amount of antibody in concentrated form has been considered as probably a sufficient total dose for the average case.

On the assumption that a given quantity of antibody would be more effective if utilized mainly against the carbohydrate in the capsule of the organism, an attempt was made to speed up the urinary excretion of the free carbohydrate present in the body by intravenous fluids containing sulfanilamide prior to the administration of serum. In this way inhibition of the organisms by chemotherapy should prevent the liberation of large amounts of free carbohydrate into the blood and spinal fluid. This method of control of the amount of specific carbohydrate present is important in the cases of average severity of a duration of 2 to 3 days or longer, and in the fulminating types in which no drug therapy has been used. The body under these circumstances theoretically con-

tains large quantities of free specific carbohydrate. In addition to the most efficient use of a given amount of antibody this speeding up excretion of free specific carbohydrate should prevent the violent reactions of the very severe forms of meningitis when a large quantity of antibody is given at one time. It has been assumed that such reactions are probably the result of the sudden uniting of large quantities of antigen and antibody. Death was frequently the result.

Since the prognosis in any form of therapy depends upon the duration of the disease prior to its administration, a brief description of the most rapid effective means of accurate diagnosis of *H. influenzae* will be given. When Gram-negative rods or even when pleomorphic diplococci, suggesting morphology of pneumococcus or meningococcus, are seen on direct smear, the possibility of *H. influenzae* should be entertained. When confusion does arise, it is due to poor Gram stains and lack of familiarity with the great variation in form of this organism. The presence of this organism may be definitely established within a few minutes when type specific rabbit diagnostic antisera are used for detecting capsular swelling of the organisms. The procedure is identical with that used for typing pneumococcus by the Neufeld method. Unless capsular swelling of the organisms is produced by type b diagnostic serum, there is no rationale for using any of the sera available, for they are active only against this type. Fortunately, almost all cases of influenzal meningitis in children are due to type b. Diagnostic typing sera are available commercially from E. R. Squibb & Sons. If no organisms are present on direct smear, 1 cc. of the purulent spinal fluid is planted in 10 cc. of Levinthal broth in a small flask. The size of surface in contact with the air is important. This is the ideal method for detecting very small numbers of *H. influenzae*. Until a definite etiology is established, sulfanilamide is given alone. When the *H. influenzae* is shown to be type b the following treatment is carried out. As soon as a continuous intravenous drip is set up, 0.1 gram per kilogram of sulfanilamide is given by infusion. After this, 0.1 gram per kilogram is given through a continuous intravenous drip over a 4-hour period in 40 cc. of Ringer's or saline, per kilogram. Following a 3-hour period of forced fluids, provided sensitivity tests are negative, rabbit antiserum in an amount containing 25 milligrams of antibody nitrogen is given intrathecally. Additional antibody is then added to the continuous drip for intravenous administration—50 milligrams of antibody nitrogen for a case of average

TABLE I

Recovered Group—Serum and Sulfanilamide								
Name	Age	Previous Duration of Illness	Drug Used	Antibody			Blood Culture	Time to Sterilize Spinal Fluid
				I V cc	I T cc	Mgm Total		
G M	19 mo	4 days	1 week	155	67	<100	0	72 hours
M W	3 yr	24 hours	11 days	180	8	<100	0	48 hours
W W	15 mo	2-6 days	1 week	140	85	<100	+	24 hours
W S	5 yr	2 days	2 weeks	0	15	<10	0	24 hours
R D	2 yr	24 hours	23 days	20	20	180	+	24 hours
A C	19 mo	5 days—P	1 week	15	5	100	0	24 hours
F J	2 yr	48 hours	8 days	15	5	100	+	24 hours
I T	23 mo	48 hours	19 days	29	10	195	+	6 days
CH B*								
J G*								
V P*								

* Complete recovery of these patients treated at other institutions has been reported but details of course have not yet been received

First, I should like to present the significant details of the eleven patients who recovered following treatment with serum and sulfanilamide (Table I). The first four patients were treated with unconcentrated serum which explains the large volume of serum used. The other seven were treated with concentrated antibody solution produced and analyzed chemically by E. R. Squibb's according to the methods which we have worked out with Heidelberger. This product is now available commercially. In five patients, the total estimated dose was given at one time with rapid and complete clearing of the meningitis. In one, small doses were given at 24-hour intervals through an error in calculation and the process was more prolonged, requiring 6 days for complete sterilization.

Table II shows the group who recovered following treatment with sulfapyridine and serum and also the group treated with serum alone or a small amount of combinations of drugs. The two patients who were treated with sulfapyridine and serum are of interest in demonstrating the inhibitory action of this drug alone for periods of 10 days or over. The clinical condition of these two patients was remarkably good considering the duration of the meningitis, so that the demonstration of organisms with ease on direct stained smears was a great surprise.

TABLE II

Recovered Group—Serum and Sulfapyridine								
Name	Age	Previous Duration of Illness	Drug Used	Antibody			Blood Culture	Time to Sterilize Spinal Fluid
				I V cc	I T cc	Mgm Total		
E A	14 mo	2½ weeks and P	S alone 3 days and then 18 days	285	90	200	+	72 hours
A 7	5 yr	10 days	P 2 weeks	200	0	100	0	48 hours
Miscellaneous Group with Serum Therapy								
K P	4 yr	48 hours	No drug	26	0	125	+	36 hours
M B *	5 yr	34 hours 10 cc 0.5% pron 30 gr I	S & T 48 hours	200	0	120	0	24 hours
R G	3 yr	4 days P and stopped	P 4 days and S 6 days	0	0	135	0	24 hours
E M *	2½ yr	24 hours	S 2 days, P 2 doses I 8 days	25	5	150	+	24 hours

S—Sulfanilamide P—Sulfapyridine, T—Sulfathiazole

* All drug discontinued because of leukopenia

The organisms were well encapsulated. The first patient was treated with sulfapyridine alone in large doses parenterally for three days in Babies Hospital without influencing the picture. Both recovered promptly on addition of serum therapy. The miscellaneous group is of great interest in that the first three had only intravenous therapy. In two of these, antibody was demonstrated in the spinal fluid. The first had no drug therapy, the second had drugs for 48 hours only and the third had no drug for a 24-hour period after the first two days, following which sulfathiazole was given in such doses that only minute amounts could be detected in the spinal fluid. Three of these patients were treated with Squibb's concentrated antibody.

Table III lists the same data for the eleven fatal cases. These have been divided into three groups. In five, serum therapy has been guided by presence of free antibody in the patient's serum (sulfapyridine has been used with serum in four of the five). In three of these the spinal fluid has become sterile, the chemistry has improved and the temperature became significantly lower when a neutropenia developed following which an exacerbation occurred with a rapid downhill course.

treatment alone, I believe serum should be combined with chemotherapy. All the theoretical evidence which I have outlined indicates that the latter treatment should materially improve the prognosis. Experimental work indicates that the combination of serum and drug in mice is more effective than the sum of the two separate effects would lead one to expect, and suggests a synergistic effect. This is logical since the inhibitory mechanism of the drug should enable smaller quantities of the antibody to be effective. The clinical experience with this type of treatment, combined drug and antibody, is still limited. This fact is definite, however. On the whole when the patient does recover under drug therapy alone, the course of the disease is more prolonged and there is greater tendency to exacerbations than when serum and drug are used in combination.

The method of combined treatment with type-specific rabbit serum and sulfapyridine which we recommend is essentially the same as that used in *H. influenzae meningitis*. One-tenth gram (0.1 gram) of sodium sulfapyridine per kilogram in 15 cc per kilogram of saline or Ringer's is introduced intravenously as soon as the meningitis is recognized to be pneumococcus which should be within a 20 minute period after the fluid reaches the laboratory in the great majority of cases. For, except in the rare extremely early case, the organisms are easy to find on direct stained smear, their morphology is quite characteristic and typing may be performed by the Neufeld method directly from the spinal fluid. During the next 4-hour period one aims to introduce intravenously 40 cc of fluid per kilogram body weight. One per cent sodium sulfapyridine in a quantity sufficient to give 0.1 gram per kilogram of the drug forms a varying portion of this volume depending upon the weight of the patient and the remainder is made up by saline or Ringer's solution. Here, too, it is hoped that the free specific carbohydrate will be excreted during this period by the forcing of fluids. The serum is administered in diluted form over a 2-hour period just as described for *H. influenzae meningitis*. In a patient with infection of average severity it is advisable to start with 100,000 units or 100 milligrams of immune nitrogen of rabbit type-specific anti-pneumococcus serum. The adequacy of such a dose may be detected by the method described previously, which tests for the presence of free anti-carbohydrate antibody in the patient's serum by the Neufeld reaction. If free antibody cannot be demonstrated, additional antibody is indicated immediately. In

obviously severe infections, until more evidence is obtained on this point, 200,000 units are indicated. Our experience with influenza meningitis and the knowledge of the specificity of sulfapyridine for pneumococcus leads us to try the intravenous route alone for serum treatment for the first 24 to 36 hours, unless the spinal fluid shows a decrease in sugar and increase in cell count. Under such circumstances spinal drainage is performed at 8-hour intervals for this period, hoping that changes in pressure relationships may increase permeability of the meninges for the antibody from the blood. Daily examination of the patient's serum for free antibody and the chemistry and cultures of the spinal fluid guide one in further serum therapy just as in influenza meningitis. Intravenous drug is continued for at least the first 24 hours. After administration of 0.2 gram per kilogram of the drug during the first 4 hours, a dose of 0.1 gram per kilogram is used during the remaining 20 hours. Following this, the oral route is used if condition of the patient permits and 0.1 gram per kilogram is used for each 24-hour period through one week after the spinal fluid has become normal. If the meningeal reaction is poor so that the first spinal fluid specimen on direct smear has the appearance of a culture of pneumococci with few pus cells, one intrathecal dose of 50,000 units is given in addition to the intravenous serum. If the criteria previously described for determining an excess of antibody are present 24 hours later, no further serum is given by any route.

MENINGOCOCCUS MENINGITIS

The comparison of the efficacy of drug and serum alone in meningococcus meningitis is very difficult at the present time. The sporadic form of the disease varies so greatly in virulence that only an epidemic would serve as a proper background for evaluation of the efficiency of each one of these forms of therapy. Under such circumstances alternate case selection on a large scale would answer the question. However, so far as present evidence goes, there is general agreement that sulfanilamide alone is equal to or superior to serum therapy. In mice, meningococci are susceptible to both drugs when used alone but sulfapyridine is effective in lower concentration than sulfanilamide.

It has just been during the last five years that an attempt has been made to put serum therapy on a quantitative basis. The agglutinin titer method for analyzing the strength of a given serum has been shown to

be very inadequate. With the production of a rabbit antiserum of high anti-carbohydrate antibody content analyzed by chemical methods and used in the manner described for the other two forms of meningitis, the mortality figures previously reported for serum therapy should be improved.

Unless an epidemic occurs there is every reason to expect the majority of patients to respond to sulfanilamide alone. For this reason, at the present time it seems advisable to start all patients on sulfanilamide first by a large infusion containing 0.1 gram per kilogram. After this, 0.1 gram per kilogram is given through continuous intravenous drip over a 4-hour period in about 40 cc per kilogram of Ringer's or saline solution. The administration of the drug is continued by intravenous drip or by subcutaneous route through the first 24 hours by giving 0.1 gram per kilogram for the remaining 20 hours. The subsequent administration of 0.1 gram per kilogram per day, divided into 6 doses at 4-hour intervals, is continued for one week after the first sterile spinal fluid is obtained. The diffusion of the drug into the meninges is so efficient that intrathecal treatment is unnecessary. However, daily lumbar punctures are recommended in order to follow the spinal fluid cell count and chemistry in order to be guided by more objective evidence than the patient's clinical condition. Experimentally drug-resistant strains are encountered frequently. If the criteria, discussed previously, fail to demonstrate marked evidence of improvement 48 hours after start of chemotherapy, serum in a diluted form should be given over a 2 to 3-hour period by a continuous intravenous drip. Estimation of the total amount of antibody necessary is difficult to assess, for experience with the use of serum has been gained when a purely volume basis was used. Mouse protection tests now used by the National Institute of Health permit the use of units. In severe forms 100,000 units should be used. The examination for evidence of free antibody in the patient's serum may be applied following the serum administration to determine whether a sufficient dose has been given. In the present state of our knowledge serum is not indicated by intrathecal route, unless objective signs of improvement fail to occur 24 hours later.

If the patient represents the fulminating type, serum therapy seems indicated after a 4-hour period of drug therapy and forcing of fluids.

The qualitative precipitin test on the cleared spinal fluid served as a valuable prognostic aid in a group of serum treated patients during

TABLE IV

THE RESULTS WITH VARIETY OF DRUG COMBINATIONS AND SERUM ANALYSIS OF 26 PATIENTS TREATED WITH RABBIT SERUM

	Recovered	Fatal	Total
Treated with Sulfanilamide	11	4	15
Treated with Sulfapyridine	2	4	6
No drug	1		1
Sulfanilamide and Sulfathiazole—48 hours	1		1
Sulfanilamide and Sulfapyridine	1		1
Sulfanilamide—2 days, Sulfathiazole—8 days	1		1
Sulfathiazole		1	1
	—	—	—
Total	17 or 65%	9 or 35%	26

an outbreak in Baltimore in 1936. Perhaps this may be of value in selecting the patients on whom serum therapy is indicated in addition to drug therapy.

The results of combined treatment in humans is too limited to warrant comparison with groups treated by drug alone. In addition, until quite recently, the national standards of potency, based on agglutination tests, prevented a quantitative approach to this type of treatment. There is general agreement that both antitoxin and antibacterial serum aid in decreasing toxicity. Mouse experimentation shows very consistent results with this type of treatment. When either sulfanilamide or sulfapyridine is combined with serum therapy, the protection is greater than the effects of the sum of the two.

SUMMARY

It has been shown that in the present state of our knowledge a combination of antibody and chemotherapy offers the best prognosis in both *H. influenzae* and *pneumococcus meningitis*. In *meningococcus meningitis* the marked susceptibility of the organism in sporadic cases to both sulfanilamide and sulfapyridine warrants a trial period with drug alone. However, in fulminating types of the disease and severe forms in infants intravenous serum is indicated after a 4-hour period of drug administration.

THE NEWER KNOWLEDGE OF VITAMIN K*

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ONE of the most dramatic and stimulating series of events of recent years concerns the discovery of Vitamin K, its isolation and the synthesis of various active compounds, the recognition of its role in the body and its clinical application in the study and treatment of deficiencies. Extensive work has been done largely in the past five or six years, and we can only touch on some of the major developments in this presentation.

Dam¹ in 1934 first postulated that the hemorrhagic disease which he and others had observed over the previous five years in chicks on a variety of purified low-fat diets was due to a deficiency of a specific antihemorrhagic factor in the diet and a year later proposed the designation of this factor as Vitamin K (Koagulations Vitamin).² This hemorrhagic tendency noted incidentally was at first attributed to scurvy, but subsequent work^{3, 4, 5, 6} indicated that this was not the case, nor was it due to lack of, or cured by any of the other then recognized accessory dietary factors.

The fact that the diets which produced the hemorrhagic tendency were of low-fat content suggested the fat-soluble nature of the vitamin, and this was subsequently proved^{7, 8, 9} when it was obtained from natural sources by extraction with fat solvents. It is found most richly distributed among the green, leafy plants and vegetables such as alfalfa, spinach, cabbage, cauliflower, kale, carrot-tops, and seaweed, and to a lesser extent in others. In general, it may be said to be most abundant in the chlorophyll-containing structures and is therefore to be found in higher concentrations in leaves than in seeds, fruit or roots. Another rich source is putrified fish meal.

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Investigation of the hemorrhagic disease of chicks due to K avitaminosis indicated that this was associated with a prolonged clotting time^{6, 10} and it was suggested¹¹ that this was due to hypothrombinemia. Dam, Schønheyder and Tage-Hansen¹² and Quick¹³ produced definite proof of this, the latter by tracing the progressive fall in the level of the plasma prothrombin in chicks on K-deficient diet which in turn was corrected by feeding the vitamin. Vitamin K deficiency of severe grade is very difficult to produce in mammals by dietary means alone in the absence of disturbances of its absorption or metabolism, although the more moderate grades can be produced on carefully extracted diets. In 1937 Greaves and Schmidt,¹⁴ who had previously shown that the absorption of the other fat-soluble Vitamins A and D was interfered with when bile was absent from the intestinal tract, were able to produce hypoprothrombinemia in rats with common duct obstruction or biliary fistula. Quick, Stanley-Brown and Bancroft¹⁵ in 1935 drew attention to the prolongation of the clotting time by their prothrombin test and suggested that the defect was primarily a diminution of this component of the clotting mechanism. Later Warner, Brinkhous and Smith^{16, 17} and others demonstrated this defect in jaundiced patients.

Since Vitamin K deficiency is synonymous with diminished prothrombin activity of the plasma, considerable importance attaches to methods for the estimation of this component of the clotting mechanism now in current use. In speaking of the plasma prothrombin we should realize that the chemical nature of this substance is unknown, although it is closely bound to the globulin fraction of the plasma. These tests merely assay the activity of the prothrombin, and thus, perhaps, indirectly indicate the amount present.

The first of these devised by Quick¹⁸ is performed as follows. Mix the contents of one capsule of thromboplastin with 5 cc physiological saline solution containing 0.1 cc (10/M) sodium oxalate. Incubate this at approximately 45° C (113° F) for 10 minutes, then centrifuge at slow speed for 10 minutes. Draw off the resultant extract with a pipette and place in a test tube or bottle. This solution of thromboplastin is stable for periods of time up to two hours. Draw 4.5 cc blood from a large vein with a large needle. Add the blood to 0.5 cc of sodium oxalate (10/M) in a centrifuge tube, mix and centrifuge at low speed for 5 to 10 minutes. Add 0.1 cc clear plasma to 0.1 cc thromboplastin in a small test tube and mix. Add rapidly 0.1 cc calcium chloride (40/M). Hold

test tube in bath at 37.5°C while tilting very gently every second or two and note the length of time in seconds elapsing before the formation of a definite clot. Normal blood shows a clotting time of 15 seconds or less. If the clotting time exceeds 18 seconds, precautionary measures should be recommended. This method has the advantage of ease of performance and is sufficiently accurate for most clinical observations.

Warner, Brinkhous and Smith¹⁹ in 1935 brought out a method which is more cumbersome and requires considerable experience for its most accurate performance, but which in the hands of many workers, including those in our own laboratory, gives more accurate and consistent results and is more desirable for research purposes. This test is performed as follows. Blood to be tested for prothrombin is oxalated with 1.5 per cent sodium oxalate in the proportion of 0.5 cc sodium oxalate to 4.5 cc of blood (1:10). It is centrifuged and 1 cc plasma to be tested is removed. To this sample 0.1 cc fresh thrombin is added to clot out the fibrinogen present. The thrombin is made by adding to 0.15 cc oxalated plasma 0.3 cc normal saline, 0.15 cc thromboplastin and 0.15 cc calcium mixture, and winding out the clot which forms in about 20 seconds. An excess of thrombin remains after the clot is removed and this is used immediately, as it disappears rapidly. After standing 15 minutes while the fibrinogen clots out, the fibrin clot is removed, leaving free prothrombin. Of this prothrombin, 0.1 cc is diluted with oxalated saline. The dilution is then added to a mixture made up of equal quantities of normal saline, calcium and thromboplastin and incubated in a water bath at 28°C for 30, 45, 90 and 120 seconds, timing from addition of dilution. After incubation, 0.1 cc of fibrinogen is added and the clotting time measured with a stop watch. The dilution for the sample tested is that one which will clot in 15 seconds when incubated for 30 or 45 seconds for dog plasma and 90 or 120 seconds for human plasma. Incubations other than the one clotting in 15 seconds must clot in time longer than 15 seconds. A normal sample is compared with other samples tested and the results are expressed in per cent of that normal.

The same authors²⁰ have more recently published a much simplified method which can be performed at the bedside or in the office and which gives results quite satisfactory for clinical purposes. The technique is as follows. Place 0.1 cc thromboplastin in a small serologic test tube. The tube is then filled to a 1.0 cc mark with freshly drawn blood from the patient. The tube is inverted once over the finger to secure com-

plete mixing and then tilted gently every second or two. The time is noted in seconds for the formation of a clot. Normal blood usually clots in 25 to 30 seconds. However, it is advisable to run a standard on normal human blood as a check. Then the percentage of normal is given as follows:

$$\text{Prothrombin Activity in per cent of normal} = \frac{\text{Clotting time of normal blood} \times 100}{\text{Clotting time of patient's blood}}$$

A more recent test has been brought out by Allen and his associates²¹ but as yet we have had no clinical experience with it.

The most accurate is the dilution method of Warner, Brinkhous and Smith, but, as it is more intricate and time-consuming, it may not find wide clinical application, as either the method of Quick or the simplified method of Warner, Brinkhous and Smith is sufficiently accurate for clinical use. In all our own work except for a few of the earlier clinical cases investigated, the dilution method was employed and in our own laboratory has an error of plus or minus 3 per cent.

The discovery of the existence of Vitamin K and of its sources led to the production of more and more concentrated extracts until Dam and his co-workers²² in 1939 reported a concentrate which assayed 20 million Dam units per gram. Similar extracts were obtained by McKee²³ and by Binkley and his associates.^{24, 25} It was then recognized that while both were very active, the Vitamin K₁ obtained from alfalfa was distinctly different from that from fish meal, which came to be called K₂. Work then began in earnest on the elucidation of the structure, and K₁ has been shown to be 2-methyl-3-phytyl-1, 4-naphthoquinone. The structure of K₂ has not yet been worked out. Almquist and Klose²⁶ reported that phthiocol, a substance which had previously been isolated from the tubercle bacillus, possessed Vitamin K activity. This, now called K₃, has a structure similar to K₁ but has an hydroxyl instead of a phetyl group attached to the third carbon atom.

In July 1939, four groups of workers^{27, 28, 29, 30} independently reported that another compound, 2-methyl-1, 4-naphthoquinone, possessed Vitamin K activity. This synthetic substance now known as K₄ is generally accepted as having the highest activity of all those so far studied, and seems indeed to be even more potent than the crystalline vitamin compounds obtained from natural sources by extraction.

It is soluble in oil but only slightly soluble in water. It can be given by mouth in either solvent as well as intramuscularly. For intravenous

use a more soluble salt is usually employed. When given by mouth, bile salts are also administered but these are of course not necessary when it is injected parenterally. Our own preference is for the injection in oil by the intramuscular route as it is free from toxic symptoms and the effect of a single dose is maintained for a considerable period—as long as eleven days in one of our cases. Intravenous injection is also well tolerated and may act slightly more rapidly, but does not seem to be quite as prolonged in its effect.

It should be emphasized that the numerical designation of the various compounds with Vitamin K activity does not indicate, as in the members of the B complex, any qualitative differences in their action. So far as is now known they differ only quantitatively.

After absorption from the intestine the vitamin is stored in the body tissues, and, no evidence has yet been presented for any endogenous origin aside from the intestinal tract. The vitamin is present in appreciable quantities in the feces of even deficient animals, its production being attributed to bacterial action, but recent experiments with isolated intestinal loops in our laboratory cast some doubt on this, as the vitamin is still present in definite amounts after the loops have become sterile. To date, however, the factor of excretion has not been entirely ruled out. Once Vitamin K is absorbed, it is intimately concerned with the production of prothrombin, and while widely distributed throughout the body, the level of the plasma prothrombin in dogs with normal livers has been shown³¹ to be a straight line function of the concentration of the vitamin in this organ.

While formerly it was thought that prothrombin was formed in the bone marrow and distributed to the blood from the platelets, this point of view has been discredited since these elements cannot be shown to yield prothrombin, and because neither the thrombopenia produced experimentally by irradiation of the bone marrow³² nor that encountered clinically in thrombopenic purpura is associated with any decrease of the plasma prothrombin. On the other hand, a mass of evidence has accumulated to indicate that the liver is the chief and perhaps the only site of formation of this substance. Thus, damage to the liver by chloroform³³ or by partial extirpation³⁴ is accompanied by a marked fall in the plasma prothrombin, and even such minor injury as gentle massage for 25 minutes³⁵ causes a decrease of as much as 25 per cent. As recovery occurs, the level of the plasma prothrombin returns to normal.

Total hepatectomy, studied independently by ourselves³⁶ and by Warren and Rhoads,³⁷ is followed by a drop in the plasma prothrombin level to below 10 per cent in 14 hours, and we have been able to show that in the absence of the liver even massive doses of Vitamin K fail to prevent this fall in any way. Thus, it is clear that for the normal effect of Vitamin K, it must not only be absorbed, but the liver must be normal for its optimum effect in maintaining the plasma prothrombin. In normal animals (dogs) the plasma prothrombin can be shown to disappear from the circulation during passage through the lungs³⁸ as in 85 per cent of our animals we were able to show an average difference of 10.6 per cent (extremes of 4 and 19 per cent) in the prothrombin levels of blood from the right and left heart. This is definitely not due to oxygenation of the blood and cannot be shown in afferent and efferent blood of any other organs.

Another important consideration is the fact that there is remarkably little difference in the plasma prothrombin levels of normal individuals, and that, even with relatively large doses of Vitamin K, it does not seem to be possible to elevate the plasma prothrombin activity as measured by these tests above the normal level. For this reason there seems to be little danger that overdosage of the vitamin will produce thrombosis. It should be stressed that Vitamin K therapy is consistently unavailing except in patients with conditions associated with diminished levels of the plasma prothrombin. It cannot be expected, therefore, to be of benefit in such diseases as hemophilia or thrombocytopenic purpura.

Let us consider, then, certain states associated with lowered levels of plasma prothrombin and the role of Vitamin K in their production and therapy. While because of their spectacular nature the severe grades of Vitamin K deficiency associated with actual hemorrhagic tendency have occupied the limelight, it is important to recognize the lesser degrees of deficiency as from them much of great importance can be learned.

As mentioned above, it is questionable whether K avitaminosis of severe grade ever occurs from purely dietary causes, perhaps because of the synthesis of the vitamin in the intestinal tract, but in association with severe nutritional conditions definite hypoprothrombinemia of moderate grade is frequently seen, which yields promptly to appropriate therapy. Similarly, intestinal drainage either through fistulae or through prolonged use of gastric or intestinal suction may prevent a sufficient absorption of the vitamin and thus may depress the level of the plasma prothrombin.

In addition, certain individuals have come under our observation in whom there seems to exist a latent or subclinical K avitaminosis in the presence of normal dietary intake which appears to be based on some defect of absorption even though bile is present in the intestinal tract. In such persons the prothrombin is usually about 60 per cent of the normal and fails to rise appreciably after the oral administration of 2-methyl-1, 4-naphthoquinone with or without bile salts. Further evidence that the defect is primarily in the absorptive mechanism is obtained by the parenteral injection of the vitamin which is promptly followed by a rise in the plasma prothrombin level to normal.

Other instances of K avitaminosis to be explained on the basis of inadequate intake or poor absorption are found in connection with the intractable diarrheas as in ulcerative colitis or in sprue. Here, contrary to the rule outlined above, the depression of prothrombin may be so severe as to fall below the critical bleeding level (about 20 per cent of normal) for the individual, and hemorrhage may ensue. Usually these cases, too, yield promptly to parenteral therapy, and the administration of the vitamin and bile salts by mouth may be helpful. We have seen several cases falling into this category and Thomas T. Mackie from the Colitis Clinic of Roosevelt Hospital reports that in 23 per cent of their cases the plasma prothrombin was definitely reduced.

The most striking type of K avitaminosis due to failure of absorption is seen in cases of obstructive jaundice. Here, due to absence of bile from the intestinal tract the fat-soluble Vitamin K is not absorbed and seriously depressed plasma prothrombin levels result. Because the body normally has a fairly large reserve of the vitamin, the fall is gradual and may not reach the hemorrhagic level for some time, but the reserve may have become depleted through insufficient intake or for other reasons so that the duration of jaundice cannot be taken as a possible indication of the plasma prothrombin level. When the prothrombin reaches the critical level for the individual, which varies somewhat but is usually about 20 per cent of normal, bleeding occurs. Such a case is illustrated in Figure 1 which depicts the course of a patient with common duct obstruction before Vitamin K therapy was available. Bleeding is particularly apt to occur after operation as Lord³⁵ has shown that manipulation of the liver such as may be required in operations on the common duct may themselves significantly lower the prothrombin content of the plasma. Thus, a patient whose preoperative prothrombin

was diminished but still above the critical level might bleed due to further depression following an operative procedure

In the absence of liver damage, the response to therapy is dramatic as illustrated by the patient's course as it appears in Figure 2

Numerous clinicians have noted that patients with varying degrees of liver damage may fail to respond adequately or at all to the administration of substances with Vitamin K activity^{17, 18 39 40 41 42} In our own series a considerable number have failed to show a satisfactory response, and as will be discussed later, this finding can be used as an index of liver damage A particularly striking clinical example of the role of the liver quite comparable to the hepatectomy experiments in animals is seen in Figure 3 which depicts the course of a 50-year old woman who was admitted to the hospital with a temperature of 40° C She had had symptoms of gall bladder disease for 18 years and had been somewhat jaundiced for 5 weeks On admission her condition was so critical that she was treated conservatively with clyses, blood transfusions and Vitamin K and bile salts for a period of 4 days and was then subjected to cholecystostomy At operation an inflammatory mass was found around the lower portion of the gall bladder overlying the common duct The administration of Vitamin K (Klotogen) was quite effective at first, and by one week after admission the plasma prothrombin was 100 per cent of normal Despite continued vitamin therapy and blood transfusions, however, it suddenly fell thereafter and remained at a low level The patient subsequently died, and at postmortem examination thromboses of the hepatic artery and portal vein with massive necrosis of the liver were found Microscopic examination of the thrombi indicated that they had been deposited at about the time that the precipitous fall in the plasma prothrombin occurred

A similar but less severe example is seen in Figure 4, showing the course of the plasma prothrombin level in a patient with cirrhosis of the liver The concentration of prothrombin here was 70 per cent before treatment with 2-methyl-1, 4-naphthoquinone, but it continued to fall even after relatively large doses until it reached 48 per cent

Severe enterocolitis or sprue with intractable diarrhea may be associated with marked depression of the plasma prothrombin level due, probably, to deficient diet or diminished absorption, or both In some of these cases the administration of Vitamin K and bile salts may be effective in overcoming the deficiency and parenteral therapy is often

strikingly so Figure 5, however, represents the course of a patient with sprue treated orally before the preparations suitable for parenteral therapy were available. There was no response, and although the amounts used here—about 5,000 units per day—were small compared to our present day dosages, they had been effective in many other types of cases.

A number of investigations indicate the presence of low plasma prothrombin levels in new-born infants and of extreme hypoprothrombinemia in cases of hemorrhagic disease of the newborn^{43, 44, 45, 46, 47, 48}. These authors, using methods other than the test of Quick, have found that the normal new-born infant has a plasma prothrombin level of from 20 to 30 per cent of that of the mother, and that in hemorrhagic cases the values are even lower. Quick and Grossman,⁴⁹ on the other hand, using Quick's method, failed to find such consistently low values in the new-born, but did find⁵⁰ a marked diminution from the first to the sixth day of life. It seems, therefore, that the prothrombin levels of normal infants are precariously near the hemorrhagic level and seem to bear a rough percentage relationship to that of the mother. In premature infants^{47, 48} the prothrombin has been found to be less than 10 per cent of that of the mother. In all infants, however, the level gradually rises after the fifth or sixth day and reaches the adult normal value at about 10 or 11 months.

While hemorrhagic disease is associated with diminished prothrombin, there cannot be said to be any definite level at which bleeding occurs. Thus, some cases may have values as low as 10 to 15 per cent without hemorrhage, while in others bleeding is seen at a somewhat higher level.

Fortunately, however, the condition can be prevented by the administration of the vitamin to the mother before delivery, and may be spectacularly cured by means of oral or parenteral therapy in the infant. Figure 6 illustrates the course of such a patient from the Pediatrics Department of the New York Hospital who was treated with 2-methyl-1, 4-naphthoquinone.

Finally, what we believe will be one of the most fruitful fields of study of Vitamin K concerns its use in the investigation of liver function. As was suggested above, the response of a subject with a normal liver but lowered plasma prothrombin, to adequate administration of Vitamin K is so prompt and so striking that it is possible to use this

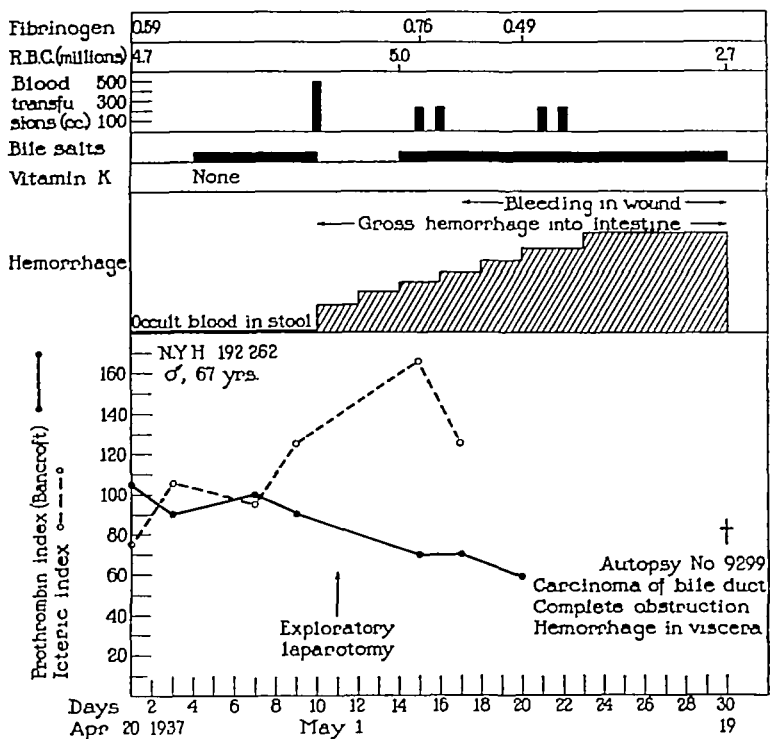


Figure 1

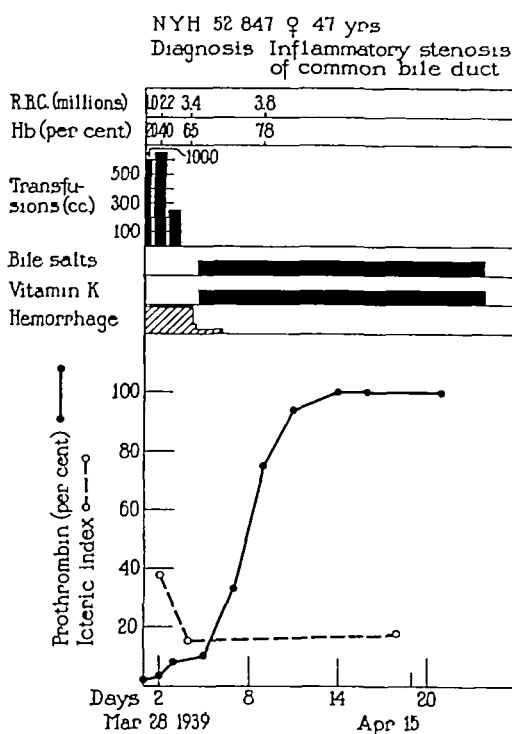


Figure 2

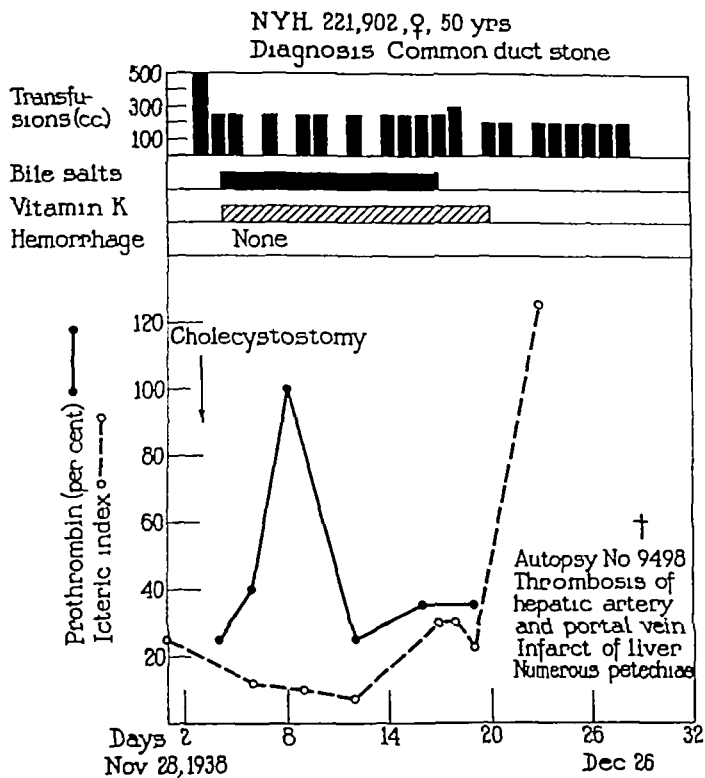


Figure 3

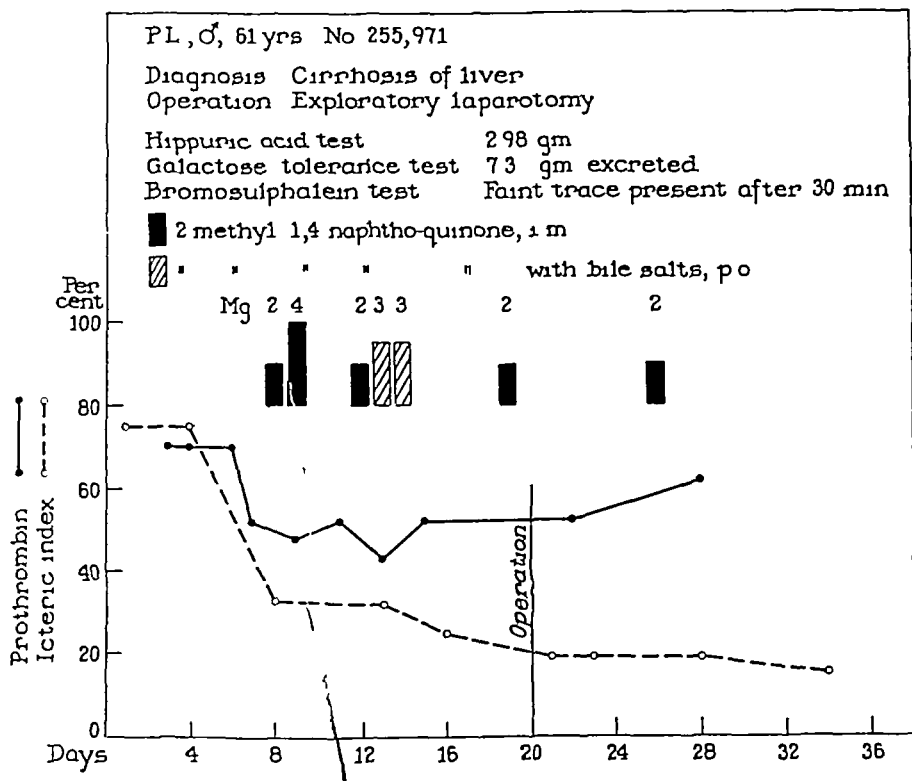


Figure 4

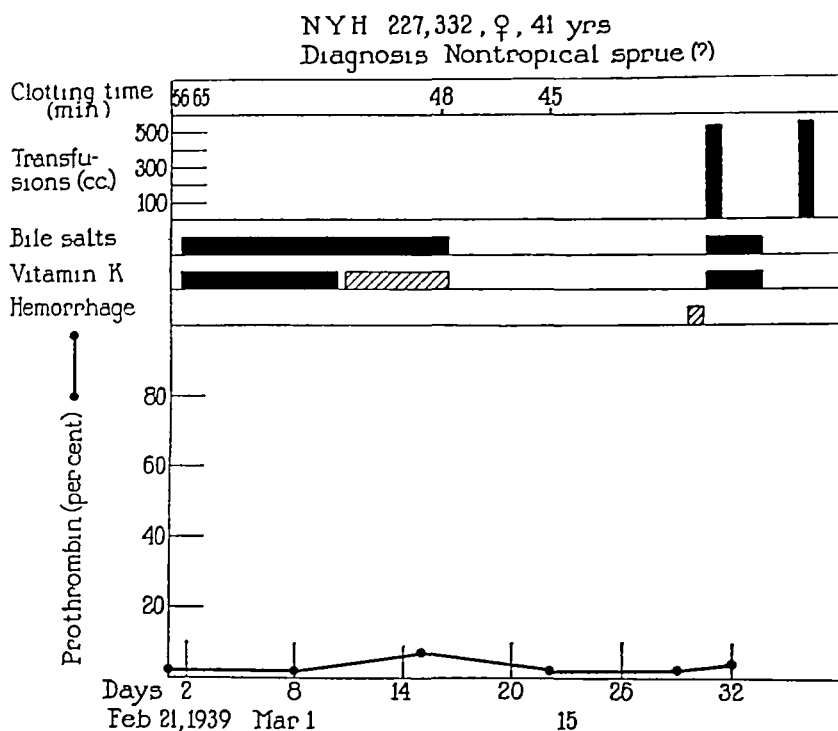


Figure 5

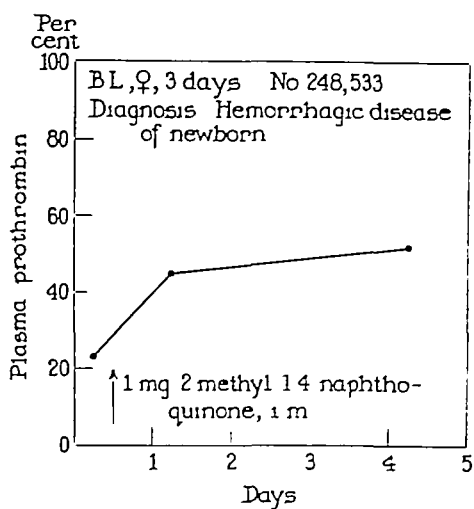


Figure 6

response as an indication of the state of the liver. Experience with this test in a considerable number of cases, including more than forty jaundiced patients, has led us to impose considerable confidence in it. Indeed, we have come to feel that it possesses certain advantages over even the best of the current tests of liver function in that—at least so far as the prothrombin-forming activity of the liver is concerned—we are enabled to distinguish between what we may call functional disturbances and those due to organic liver disease. It seems fair to say that within limits, the level of the plasma prothrombin, if previously depressed below 80 per cent, indicates the performance of the liver, while the response to Vitamin K—in our studies to the intramuscular injections of 2 mgm of 2-methyl-1, 4-naphthoquinone—indicates whether the diminished prothrombin was due to functional disturbances, such as inadequate intake or absorption, or to organic disease. The test finds one of its greatest fields of usefulness in distinguishing between jaundice of extrahepatic origin—due, for example, to obstruction of the common duct by tumor or stone—and that due to parenchymal liver disease. In brief, we have found that in the former the plasma prothrombin either remains above 80 per cent, or, if it be depressed, rises following the intramuscular injection of 2 mgm of 2-methyl-1, 4-naphthoquinone by more than 10 per cent in the first 48 to 72 hours. In intrahepatic jaundice the prothrombin, which here is uniformly depressed, either fails to rise by this amount or continues to fall. In forty jaundiced patients, twenty-five of whom were suffering from common duct obstruction of one sort or another and in fifteen of whom the icterus was due to catarrhal jaundice, cirrhosis, liver abscess, etc., the test was almost 100 per cent correct. The findings were checked by operation or post-mortem examination in all cases of extrahepatic jaundice and in nine of those in whom it was of intrahepatic origin. The remaining six patients followed clinical courses typical of catarrhal jaundice.

Further applications of this test remain to be studied, but work now in progress suggests that its simplicity and accuracy may prove very useful in studying alterations in liver function in a wide variety of conditions.

TABLE I
EXTRAHEPATIC JAUNDICE—COMPARATIVE ACCURACY OF TESTS

<i>Type of Test</i>	<i>Authors</i>	<i>Total No of Cases</i>	<i>Cases with Normal Response</i>	<i>Per Cent Correct</i>
I Galactose Tolerance	Schiff & Senior	21	20	95%
	Banks, Sprague & Snell	68	41	60%
	White	12	11	92%
	Lord & Andrus	7	4	57%
II Serum Phosphatase	Rothman, Meranze & Meranze	29	25	86%
	Cantarow & Nelson	31	21	68%
III Hippuric Acid	Quick	3	2	67%
	Snell & Plunkett	12	2	17%
	Lord & Andrus	6	6	100%
IV Flocculation	Hanger	25	25	100%
V Response of Plasma Prothrombin to 2-Methyl-1, 4-Naphthoquinone	Lord & Andrus	25	25	100%

TABLE II
INTRAHEPATIC JAUNDICE—COMPARATIVE ACCURACY OF TESTS

<i>Type of Test</i>	<i>Authors</i>	<i>Total No of Cases</i>	<i>Cases with Abnormal Response</i>	<i>Per Cent Correct</i>
I Galactose Tolerance	Schiff & Senior	65	63	97%
	Banks, Sprague & Snell	31	17	55%
	White	34	25	74%
	Lord & Andrus	9	7	77%
II Serum Phosphatase	Rothman, Meranze & Meranze	24	18	75%
	Cantarow & Nelson	22	12	55%
	Lord & Andrus	2	1	50%
III Hippuric Acid	Quick	13	12	92%
	Snell & Plunkett	6	4	67%
	Lord & Andrus	6	4	67%
IV Flocculation	Hanger	33	33	87%
V Response of Plasma Prothrombin to 2-Methyl-1, 4-Naphthoquinone	Lord & Andrus	15	15	100%

TABLE III—JAUNDICE OF EXTRAHEPATIC ORIGIN

No	Case	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change
					Initial	2 1/2 Hr	48 Hr	72 Hr	
1	J B	Common Duct Stone	2 days	62	57	61	—	65	+ 8*
2	R A	Ca Head of pancreas	3 wks	50 (2nd Adm)	68	—	77	72	+ 9*
3	L H	Common Duct Stone	2 wks	16	70	80	—	—	+28
4	M P	Obstr Jaundice due to Ca	2 days	30	78	—	—	88	+10
5	J M	Ca Head of Pancreas	2 wks	150	75	85	100% in 96 hours)	—	+10
6	M P	Common Duct Stricture	off & on	75	61	72	—	73	+12**
7	L B	Cholelithiasis	off & on	30	68	83	—	—	+15
8	P D	Cholecystitis	2 wks	150	52	52	—	70	+18
9	F G	Ca Head of Pancreas	3 mos	60	66	85	—	—	+19
10	R M	Common Duct Stone	2 days	33	76	95	—	95	+19
11	I G	Cholangitis, Subacute	1 day	47	68	85	—	89	+21**
12	J I	Cholecystitis & Pancreatitis	2 days	50	75	—	100	—	+25

* These patients were operated upon immediately after the initial prothrombin was run. The effect of the operative trauma influenced the rise.

** These patients received more than one dose of 2 methyl 1,4 naphthoquinone.

TABLE III (Continued)—JAUNDICE OF EXTRAHEPATIC ORIGIN

No	Case	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change
					Initial	After Injection			
						24 Hr	48 Hr	72 Hr	
13	K H	Cu Head of Pancreas	3 wks	62	48	75	—	—	+27
14	I M	Acute Cholecystitis, Cholangitis	4 days	—	52	80	—	80	+28
15	C G	Cholelithiasis	2 wks	26	52	75	80	—	+28
16	C D	Cholangitis	3 yrs	75	68	82	100	—	+72
17	R S	Common Duct Stricture	1 mo	125	52	71	71	90	+38**
18	S P	Cu Head of Pancreas	6 mos	31	61	71	100	—	+39**
19	B O	Pancreas	1 wk	28	60	—	—	100	+40
20	R I	Acute Cholecystitis, Cholangitis	3 days	150	38	—	80	—	+42
21	M G	Acute Cholecystitis	1 mo	150	47	78	—	95	+48
22	K F	Common Duct Stone	1 wk	25	52	—	100	—	+48
23	P S	Common Duct Stricture	3 wks	150	18	67	50	—	+49
24	P P	Cholelithiasis	off & on	75	38	80	87	—	+49
25	D O	Cholecystitis	3 mos	150	38	70	—	100	+62

* These patients were operated upon immediately after the initial prothrombin was run. The effect of the operative trauma influenced the rise.

** These patients received more than one dose of 2 methyl 1 naphthoquinone.

TABLE IV—JAUNDICE OF INTRAHEPATIC ORIGIN

No	Case	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change
					Initial	After Injection			
						24 Hr	48 Hr	72 Hr	
1	A G	Cirrhosis with Hepatitis	9 days	200	48	14	—	14	—34
2	J D	Cirrhosis with Central Necrosis	2 days	—	52	48	—	33	—19
3	F S	Cirrhosis	—	12	35	—	—	25	—10
4	P L	Cirrhosis	2 wks	75	52	43	—	52	—9
5	L J	Hepatic Insufficiency	Unknown	60	41	—	36	—	—5
6	E F	Catarrhal Jaundice	3 days	107	71	—	70	—	—1
7	D M	Catarrhal Jaundice	3 wks	71	66	68	65	—	—1
8	L E	Catarrhal Jaundice	10 mos	50	23	23	—	22	—1
9	G G	Liver Abscess	4 days	75	52	—	—	52	0
10	M S	Catarrhal Jaundice	2 wks	60	67	—	68	—	+1
11	M K	Cirrhosis	—	12	39	—	37	40	+1
12	T H	Multiple Liver Abscesses	—	14	48	52	—	52	+4
13	J K	Cirrhosis	8 days	46	32	—	—	38	+6
14	S M	Catarrhal Jaundice	3 wks	100 225	70 76 52	— 76 —	— — 52	76 — —	+6 0 0
15	C M	Subacute Hepatitis	10 days	40	60	60	70	65	+10

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MASSIVE DOSE CHEMOTHERAPY BY THE INTRAVENOUS DRIP METHOD*

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INTRAVENOUS introduction of drugs, in the experimental animal, was first employed in 1665 by Robert Boyle,¹ the physicist, and Christopher Wren,¹ the architect, following the discovery by William Harvey² of the circulation of blood. A year later, Richard Lower³ practiced direct transfusion of blood from one to another animal. In 1667, Denis⁴ transfused sheep blood into man. The severe and fatal reactions, so readily understood today, resulted in legal condemnation of blood transfusion in humans.

Throughout the Eighteenth and Nineteenth centuries, blood transfusion remained in disuse though, in the Restoration Period, phlebotomy was liberally practiced, as the art and literature of those times amply attest.

Many of the technical problems relative to intravenous therapy were solved in the years that lapsed between the early experiments and the researches of the Twentieth century. The science of bacteriology was born. Asepsis was practiced in the preparation of solutions, materials, and the technical procedure. Venipuncture was simplified by the introduction of hollow steel needles, which replaced the ancient quills and cannulae.

The Development of Intravenous Infusion In 1831, Latta⁵ employed intravenous saline solution in the treatment of Asiatic cholera. During the succeeding half-century, saline infusions continued to be employed fitfully and irregularly. Reactions must have been severe and numerous, due to bacteriologic and chemical impurity. With the introduction of asepsis and improvement in chemical methods, these latter hazards were overcome and interest in intravenous infusion was stimulated.

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THE ADVANTAGES OF THE INTRAVENOUS ROUTE OF ADMINISTRATION

In laboratory experiments as well as in clinical therapy, the intravenous route of administration is the most direct, effectual and practicable method for the introduction of soluble preparations into the circulating stream. Intraarterial and intracardiac^{6,7} injections are technically difficult, more apt to be dangerous and accompanied by hemorrhage. Their use should be reserved for special circumstances, such as recent and sudden cessation⁸ of the circulation when resuscitation yet may be possible. Enteral, subcutaneous and intramuscular injections result in (1) Delayed entrance of the vehicle into the circulating fluid through uncertain and irregular absorption, (2) local inflammation from the deposition of irritant material in connective tissue or muscle, (3) mechanical limitation of the bulk of the agent to be introduced parenterally, through painful and awkward clyses, (4) possible modification through digestive or oxidative phenomena, or even destruction of a potent agent prior to its entrance into the circulating stream, (5) difficulty in obtaining, maintaining or rapidly calculating the effectual concentration in the blood of the potent agent, except in rare instances, e g, the derivatives of sulfanilamide⁹

DISADVANTAGES OF INTRAVENOUS THERAPY

Despite the advantages of intravenous therapy, several deterrents limited its usefulness. There was the purely technical difficulty of venipuncture and the local inflammatory changes incident thereto. Of more importance were the untoward sequelae, often dangerous and occasionally fatal, which occurred during or immediately after intravenous injection. These are not attributable pharmacologically to the specific drug action of the injected substance. So great was the fear of these sequelae that Sollmann¹⁰ wrote "Intravenous injections should be avoided for they always imply a greater risk to the patient than do the other methods of administration" ***** "The danger is not so much in errors of the surgical technique, which is generally rather simple, but in the fact that the injection of a foreign substance into the blood stream alters the equilibrium of its colloids and thus may result in alarming and even fatal reactions" ***** "Almost all substances may apparently produce such reactions in some individuals under conditions that are not understood and cannot be foretold" (Hanzlik and Karsner,¹¹ Hanzlik, De Eds and Tantor¹²)

The untoward reactions following intravenous therapy have given rise to many investigations and much speculation. Pyrogenic substances¹³⁻¹⁴ have been isolated and described. Alterations in temperature or hydrogen-ion concentration¹⁵ of the infusates have been held culpable. The mechanism of "colloidoclasia" has been postulated. The resemblance of the symptomatology to anaphylaxis gave origin to the concept of an "anaphylactoid" phenomenon.¹⁶ A mechanical factor such as acute dilatation of the heart¹⁷ has been suggested. Embolization¹⁸ has been suspected. Syphilologists, employing the arsenicals, coined the phrase "nitritoid crises" as their contribution to the pathogenesis of these unpleasant toxic phenomena.

Reactions occurred irregularly and were unpredictable. Clinicians felt a sense of insecurity about intravenous medication. Particularly in desperate situations of clinical practice, where vigorous therapy was clearly indicated, intravenous medication was withheld or performed hesitantly through fear that untoward phenomena might snap the thin thread by which life was, at least for the time, suspended. The problem of the untoward sequelae associated with intravenous injection was clouded in mystery.

THE VELOCITY FACTOR IN INTRAVENOUS THERAPY

In the United States, the pioneer in modern intravenous therapy was Rudolph Matas. Matas¹⁹ gave the first intravenous infusion with physiological saline solution on July 12, 1888 at the Charity Hospital in New Orleans. In 1891, appeared his first publication, citing nineteen clinical experiences with *slow* intravenous infusion. The indications for therapy were shock, hemorrhage and exhaustion. The technique differed from current practice in that vessels were exposed, ligated and cannularized rather than entered by direct venipuncture. M. Friedman,¹⁷ of Langersdreen, was probably the first continental exponent of intravenous infusion, though his earliest publication concerning "Dauerinfusion" did not appear until 1913, more than twenty years after the published record of Matas. Friedman was prompted to devise and adopt the drop method through an erroneous concept of acute dilatation of the heart. It is historically interesting to quote from a recent letter of Dr. Matas,²⁰ who writes: "If we extend the period of my experience with the intravenous method from June, 1888, when I administered the first infusion at the Charity Hospital, to the present moment (July, 1939) we realize

that a little over a half century has elapsed between these dates, during which the whole history of intravenous therapy, including remedial injections, infusions, "drip" and blood transfusions, has been evolved, developed and matured from its primitive, timid and rare beginnings to its present surpassing importance in contemporary medical practice "

"It is interesting to note as an illustration of the extraordinary pace of modern scientific achievement that this relatively new chapter in surgical history, in all its practical utility and vast therapeutic significance should have come into existence and fulfilled its most visionary realization within the span of a human life, in fact, well within the period of my own professional life and activities "

In 1923, after a lapse of thirty-two years, Matas²¹ again reported on massive infusions of saline solution and, for the first time, used the term "intravenous drip " The continued intravenous drip by regular drop instillation into the veins (phleboclysis) first came into use on his services at the Tuoro Infirmary and later at the Charity Hospital in the fall of 1910 At first (1910-1911), Matas writes "The intravenous drip was used timidly and tentatively for critical cases only, in which proctoclysis and hypodermoclysis could not be depended on for prompt and continued action " The transfer from the rectal to the intravenous drip was not made "until after long hesitation in fear of thrombophlebitis, embolism by air or clot, cardiac dilatation and pulmonary edema from venous depletion " Matas stressed the factor of velocity, recognizing that rapid injection was capable of producing toxic phenomena He advocated a rate of 40 to 60 drops per minute for the introduction of physiological saline or 5 per cent dextrose solution Following Matas, the next great proponent, in America, of the slow intravenous drip, was Hendon,²² who estimated that infusions should be paced at a rate of 200 cc of fluid per hour He described toxic phenomena arising from rapid introduction as the result of milking the tube He noted that slow rates of flow eliminated untoward phenomena He increased the indications for the use of intravenous infusion to include emesis gravidarum, grave icterus, ulcerative colitis, bleeding ulcers, intestinal obstruction and liver abscess Both Matas and Hendon were concerned with the velocity factor, essentially from the standpoint of the etiology and prevention of untoward reactions

Despite the clarity of their presentation and the accuracy of their observations on velocity, the work of Matas and Hendon did not obtain

wide currency or acceptance. The importance of velocity in intravenous injection was so little heeded that the Committee on Intravenous Therapy²³ appointed by the American Medical Association, in 1927, had only the following to say concerning rapid injections: "The rapid administration introduces several hazards, (1) the danger of overwhelming the heart and circulation with too great a volume of fluid, (2) the risk of breaking down some compensatory mechanisms as those which maintain the reaction of the blood, its osmotic tension, viscosity and the like within the narrow limits of normality, and (3) the likelihood of carrying the drug in too high concentration." The first hazard referred to the "bulk phenomenon" (v1), the second and third statements were unsupported by any clinical or laboratory observations. No mention was made of the observations of Matas and Hendon. No definition of velocity was advanced. The text books on pharmacology, in discussions of intravenous injection, were silent on the effect of velocity, except for Sollmann¹⁰ who in 1927 wrote: "A primary fall in blood pressure is apt to occur with all kinds of intravenous injection ***** [This] has been an annoying complication of experimenters on animals and no less annoying in clinical practice."

In 1929, Keith²⁴ summarized the literature on the physiological principles and therapeutic applications of intravenous medication. Concerning velocity he wrote: "The rate of injection of intravenous solution is often too rapid. From 30 cc to 40 cc each minute is a satisfactory rate when a considerable amount of fluid is being injected." The work of Matas was neither quoted nor mentioned. The toxic phenomena, due to rapid introduction of pharmacologically inert substances, were unnoted. The "satisfactory rate of administration" was ten times that suggested by Matas.

SPEED SHOCK

In 1931, my colleagues and I¹⁵ produced and described "speed shock." We demonstrated that the "rapid intravenous introduction of pharmacologically active or inert chemicals, drugs and biologic fluids may frequently give rise to immediate and far-reaching non-specific sequelae, at times serious, and occasionally fatal." "Speed shock" was produced, in the laboratory, in cats, dogs, rabbits, and monkeys. Both anesthetized and unanesthetized animals were used. Injections were commonly made into the femoral vein. In the unanesthetized animal, the

fluid was introduced through venipuncture. In the anesthetized animals, the vein was usually prepared with a cannula. Amounts of fluid of less than 5 cc were delivered into the vein or cannula with the greatest possible speed by means of syringe. Larger quantities of fluid were permitted to run in, by gravity, from an ordinary 25 cc buret. With the buret the rate of speed varied from 3 to 10 cc per minute. During the experiments, carotid blood pressures were recorded on the kymogram. Usually the respiratory tracing was superimposed. The experiments were planned so that after the animal recovered from the operative procedure, "speed shock" was obtained by rapidly introducing one or two cubic centimeters of the substance under investigation. No attempt was made to resuscitate the shocked animal. If spontaneous recovery ensued, the animal was given a slow infusion of a large amount of the substance that had produced the shock in order to eliminate the possibility that the reaction obtained was specific to the substance, any impurity contained therein, or any imperfection in the apparatus. Following this, "speed shock" was again induced by rapid injection. Each substance was tried on at least three different animals.

The clinical syndrome of "speed shock" occurred 40 to 60 seconds after injection. The symptoms included salivation, vomiting, diarrhea, dyspnea, muscle atony, muscle spasm, or sudden death. Inconstancy and inconsistency in symptomatology were the rule. In fact, it was this irregularity in response that led to the belief that some non-specific variable was the cause of our inability to work out the toxicology and pharmacology of a group of melanins under investigation at the time this work was done.

The most dramatic manifestation of "speed shock" was the rapid and precipitous fall in blood pressure which might be fatal or from which recovery might speedily ensue. Coincident with the circulatory phenomena occurred respiratory distress. There might be simple dyspnea or apnea. At times the lungs collapsed but again, as the result of severe bronchospasm there might be a ballooning of the chest. The circulating blood was rendered non-coagulable. The shock reaction preceded the blood changes.

At autopsy, the lungs were atelectatic or emphysematous. Large fresh thrombi were present in the pulmonary veins. Multiple punctate hemorrhages occurred in the abdominal viscera.

Where recovery followed a "speed shock," less tempestuous changes

could be produced, both in the circulatory and respiratory phenomena, by speeding up or slowing the rate of infusion, confirming a clinical observation of Hendon,²² who noted these changes as the result of milking the intravenous tube

The factors that modified "speed shock" seemed to be related to the concentration of the solution and the size of the molecule. Larger molecules and hypertonic solutions more consistently produced shock. It was more difficult to "shock" with viscous substances such as acacia. If a small volume of fluid such as 1 to 2 cc did not produce shock, a larger amount such as 5 cc was more likely to be efficacious. The more rapid the injection the more certain the production of "speed shock."

Repeated shocks could be produced with each of the substances studied except sodium bicarbonate and the calcium salts. Occasionally, there was a short period following shock in which the reaction could not be obtained but certainly there was nothing suggesting significant immunity. The simultaneous use, in another vein, of an infusion of acacia made it more difficult to produce shock with any given substance. This protection was not absolute.

There was apparently no species idiosyncrasy in "speed shock" for the reaction could be obtained in cats, dogs, monkeys, and man. Morphine and the anesthetics were unimportant factors since the syndrome was produced in unanesthetized animals. Pyrogenic substances in the diluents could be excluded as the sole factor since slow infusions of each shock substance could be performed with impunity. Shock could be produced equally well whether blood pressure was at a normal or subnormal level. The thermal factor was insignificant, for identical reactions occurred whether the fluids injected were ice cold or warmed to body temperature. The role of protein split products was investigated by subjecting fluids to dialysis. Dialysates reacted identically with the whole product or the bag residue.

THE SLOW INTRAVENOUS DRIP

The obvious antidote to "speed shock" was the slow infusion or "intravenous drip." In the clinic there was considerable variation in the definition of what constituted slow injection. Keith²⁴ employed 30 to 40 cc per minute as a "satisfactory rate of injection" for dextrose. Osborne,²⁵ in his text book, defined injection of one quart in 30 minutes, or 30 cc per minute as a slow injection. The Committee on Intravenous

Therapy²³ of the Council of Pharmacy of the American Medical Association quoted the workers at the Mayo Clinic, who regarded 10 to 20 cc per minute as a slow rate of injection for water, salt and dextrose. Matas,²¹ Hendon,²² Titus,²⁶ and Friedman¹⁷ employed rates of 2 to 5 cc per minute. The clinical concept of slow intravenous injection, therefore, included a range of from 2 to 40 cc per minute. In the laboratory, on experimental animals, Hanzlik and Karsner²⁷ advocated a rate of 3 cc per minute.

Reversing the experiments used in the production of "speed shock," an attempt was made to introduce all of the tested substances in such velocity as not to cause significant circulatory or respiratory reaction. No one rate was applicable to all substances. Powerful drugs could not be given at the same rate as physiological salt solution. Hypertonic solutions had to be given more slowly than isotonic solutions and large molecules more slowly than small molecules. Highly toxic substances such as copper sulphate had to be given intermittently as well as slowly. The findings suggested a rate of 1 cc per minute as a standard in pharmacologic assay. For clinical purposes, the rate, described by Matas²¹ and Hendon,²² of 2 to 4 cc per minute seemed the upper limit for amounts of 100 cc or more and 1 cc per minute for smaller amounts, particularly if the fluid was a potent biologic substance, such as a serum or a powerful drug. If "speed shock" should prove to be the preponderant cause of the untoward phenomena that accompany or follow intravenous injection, the slow intravenous drip should abolish these irregular and mysterious symptoms as well as "anaphylactoid," "nitritoid" and hemoclastic crises, post-transfusion reactions (not due to incompatibility), peptone shock, acute dilatation of the heart, and sudden deaths that occasionally follow intravenous medication.

THE THERAPEUTIC USES OF THE INTRAVENOUS DRIP

The intravenous drip was immediately utilized in the management of a large variety of conditions. These include

- 1 The relief of tissue hypohydration
- 2 The restoration and maintenance of the volume of the circulating fluid
- 3 As a method of increasing blood viscosity
- 4 As a means of dehydrating certain specific tissues by the exhibition of hypertonic solutions

- 5 For the restoration and maintenance of corpuscular volume
- 6 To supply the metabolic needs of the tissues in general
- 7 For the introduction of immune substances
- 8 For the immediate introduction of pharmacologic agencies
- 9 As a prophylactic and supportive in surgical procedures
- 10 As a convenient form of therapy for postoperative complications
- 11 In the medical management of hemorrhagic conditions, shock and metabolic disorders (Hyman and Hirshfeld,⁴² Hyman and Touroff⁴³)

INTRAVENOUS DRIP CHEMOTHERAPY

The technique of the intravenous drip has opened a new chapter in chemotherapy. The concept of "speed shock" gave rise to the suspicion that the untoward reactions occurring in chemotherapy might not be specific to the drug but technical in their origin. The goal of the chemotherapist had never been achieved, due to the serious and even fatal phenomena that resulted from effective doses of agents such as the arsenicals in syphilis. These untoward reactions resulted either in the abandonment of the chemotherapeutic approach or, as in the treatment of syphilis, in the use of divided doses spread over a period of months or even years.

If the concept of "speed shock" were correct and the immediate toxic effects that followed the introduction of chemotherapeutic agents were technical rather than pharmacological, potent therapeutic agents might be administered "in doses far greater than at present employed, and this without serious damage to the cells of the host."¹⁵ Abolition, by the intravenous drip, of the immediate toxicological phenomena might result in an approach to the goal of massive sterilization. These concepts have reached practical fruition in studies with the sulphonamides and the arsenicals.

INTRAVENOUS CHEMOTHERAPY WITH SULFONAMIDE DERIVATIVES

The introduction of the newer sulfonamides has increased interest in chemotherapy. In the vast majority of patients effective sulfonamide therapy can be maintained by oral administration. Parenteral or intravenous injection is reserved for (1) patients who are moribund or uncooperative, (2) those with fulminating infection in whom a high blood level must be rapidly obtained, (3) patients who are so disturbed

by the emesis common to the administration of these drugs that the oral administration must be discontinued, (4) those rare instances where an effective blood level cannot be reached despite adequate oral dosage. Clinical studies employing intravenous sulfonamide, particularly in pneumonia, have been reported by Marshall and Long,²⁸ Sadusk and Blake²⁹

The intravenous injection of sulfonamides may be accomplished with a small volume of a highly concentrated solution or a continuous intravenous drip of a dilute solution. The former plan has many disadvantages. It requires repeated injections. The concentrated solutions are usually locally irritating. The blood concentration that is produced by repeated injection is rapidly attained and equally rapid in its decline.

The intravenous drip method of chemotherapy is to be highly recommended in the use of sulfonamides. Sulfanilamide, itself, may be given in 0.8 per cent, sodium sulfapyridine and sodium sulfathiazole in 5 per cent concentration.

In unpublished work performed on the Service of Max Pinner at the Montefiore Hospital, Gary Zucker³⁰ has initiated some interesting observations concerning intravenous drip chemotherapy with sulfanilamide.

Using an 0.8 per cent solution in isotonic sodium lactate, 1200 to 1600 cc., containing 10 to 15 grams of the drug, were injected between 9 A.M. and 7 P.M. The blood level, which could be made to vary with the rate of injection and the total amount administered, reached 16 to 26 mgm. per cent within four hours. This concentration could be maintained until the infusion terminated. In the morning when the drip was again set up, after a lapse of approximately twelve hours, the level was still at 10 mgm. per cent. In the course of five days patients received approximately 60 grams of the drug intravenously. Only a very small percentage of the sulfanilamide was acetylated, the largest portion, perhaps 85 to 90 per cent, circulating as the effectual free form. These concentration curves follow closely those prepared by Sobotka for blood arsenic in massive dose chemotherapy of syphilis.

This high concentration was maintained without marked objective toxicology though subjectively the patient suffered considerably from the familiar cerebral manifestations. Blood counts showed a fall of hemoglobin of 10 to 20 per cent. The urine revealed crystals but was free from manifestations of kidney irritation.

The easy assimilation of these drugs enterally has overshadowed the results of intravenous use. Whether more can be accomplished clinically with the sulfonamides by the maintenance of these higher levels of concentration remains yet to be seen.

In exigencies where specific serum is available, as in pneumococcus pneumonia, the drip may deliver alternately the chemotherapeutic or the specific serotherapeutic agency.

INTRAVENOUS ARSENOTHERAPY

The bulk of our experience in massive dose intravenous drip chemotherapy has been with arsenicals in the treatment of primary and secondary syphilis. Since 1931, with Louis Chargin and William Leifer,^{31 32 33 34 35} more than four hundred patients have been treated. Over a span of five days neoarsphenamine has been given in 4 gm doses, Mapharsen up to 1200 mg doses. The toxic phenomena and the therapeutic efficacy may now be compared with the results of routine therapy.

The Toxic Phenomena The first consideration in chemotherapy is concerned with risk. In clinical medicine the patients whose life is not in immediate jeopardy must not be exposed to hazardous therapy (*noli nocere*). How then does the toxicology of massive dose arsenotherapy compare with that experienced in routine treatment?

Mild and grave toxic phenomena result from all types of arsenotherapy. Of the mild phenomena, to be considered only for their nuisance value, are encountered primary and secondary fever, toxicodermata, an occasional instance of transitory jaundice, and gastrointestinal distress (nausea and vomiting).

The primary fever, occurring on the first day of treatment and lasting but a few hours, has been present in 62 per cent of the patients receiving neoarsphenamine—41 per cent of those in the Mapharsen series. How commonly this occurs in routine therapy cannot be estimated. Moore³⁶ uses the word, "usually." In the routine ambulatory clinic, where the patient is sent home following the injection, there seems to be no way of estimating the frequency of primary fever. Parenthetically, it may be said in this place that one of the grievous short-comings of the literature of the syphilologists is the paucity of information concerning untoward symptomatology. The published information is sketchy, to say the best. There are wide discrepancies

between the statements of the most eminent workers in this field

The secondary fever, usually associated with toxicodermata (clearly to be differentiated from the ominous dermatitis exfoliativa) occurred toward the end of treatment in 64 per cent of the patients in the neoarsphenamine group and 12 per cent of those receiving Mapharsen. The occurrence of this complication in routine therapy is not stated.

Renal damage did not occur in any patient. There were daily urine examinations and estimations of renal function by all available methods before and after treatment. Stokes³⁷ states that renal damage occurred in 10.7 per cent of those receiving routine treatment.

Mild transitory jaundice was seen in 3.6 per cent of the neoarsphenamine series—0.7 per cent of the Mapharsen group. Tests of liver function were done by Louis J. Soffer before and after treatment. The urine was examined daily for urobilin. Moore³⁶ states that jaundice is "fairly frequent" in routine therapy.

As to nitritoid crises, there were none. Moore³⁶ places their incidence as 0.1 to 0.5 per cent. According to Stokes,³⁷ they occur in 20.8 per cent.

Grave Toxic Phenomena. Of the grave toxic phenomena in skin, blood and liver, there was a single instance of dermatitis exfoliativa with recovery. Even this complication was questionable since the patient also received sulfanilamide for a subsequent gonorrheal infection. With this exception there has not been experienced any severe dermatosis, any of the blood dyscrasias such as aplastic anemia or granulopenia, any degenerative hepatitis or nephritis. In routine treatment, Moore³⁶ states that dermatitis exfoliativa occurs 1/126 with arsphenamine—1/197 with neoarsphenamine. Stokes³⁷ gives a "fraction of a per cent" for blood dyscrasias. Moore³⁶ has experienced hepatitis with arsphenamine 1/117, with neoarsphenamine 1/282. If these three complications did not each occur in the same patient the incidence of their presence in the patients treated routinely, according to the Moore figures, must be between 1 and 2 per cent. Since these complications result fatally in more than half of the sufferers, it would indicate an expected treatment mortality for routine therapy approximating 1 per cent.

Peripheral neuritis occurred in 35 per cent of the patients who received neoarsphenamine and 1 per cent of those treated with Mapharsen. Vitamin B₁ and C did not affect the incidence or severity of the neuritis. In the Mapharsen series the neuritis was mild. In no instance

was it incapacitating. In routine therapy peripheral neuritis is "fairly frequent."

The single important toxic phenomenon of grave significance experienced in massive dose chemotherapy has been hemorrhagic encephalitis. Cerebral symptoms have occurred in just short of 2 per cent of the patients. Twice the complication was exceedingly grave, one of the men was unconscious for several days, the other died.

In routine therapy there is a diversity of opinion concerning the incidence of hemorrhagic encephalitis. Moore³⁶ in 15,000 patients has never seen it. Schamberg³⁸ reports its incidence "many times." Cole³⁹ experienced fatal hemorrhagic encephalitis once per two hundred patients. It is his opinion that it causes 62 per cent of all treatment deaths.

Hemorrhagic encephalitis is not produced by overdosage. It occurs as an idiosyncrasy and in routine treatment usually follows a second or third injection. In addition to its incidence in fatal cases, it must occur also in individuals who recover. We can obtain no data on this point from the syphilologists.

Hemorrhagic encephalitis is the greatest threat in massive dose chemotherapy. It is a manifestation of idiosyncrasy, not overdosage. It has been experienced by most syphilologists in routine therapy as frequently as in our series. Moore's experience is apparently unique and beyond our understanding. One hundred per cent of our complications are reported. Is this equally true of routine therapy where patients are ambulatory and the case loss averages 84 per cent?

In our experience, "treatment death" has occurred once in more than four hundred experiences (0.25 per cent). There has been no death in the Mapharsen group. In routine therapy, Cole³⁹ had twelve treatment deaths, 1 per cent in a series of 1212 patients. More than half of these, approximately a half of 1 per cent, resulted from hemorrhagic encephalitis. Stokes,³⁷ as well as Phelps⁴⁰ in the Navy, has had one treatment death per five thousand to seven thousand injections. If each patient received approximately twenty-five injections, the ratio of treatment death is one to three hundred, or one to four hundred. In comparison, treatment death of 1 per cent in our neoarsphenamine series is but slightly excessive. The mortality of 0.25 per cent in the whole series parallels the routine experience. The record of no treatment death in the Mapharsen series speaks for the relative safety of massive dose chemotherapy.

THE RESULTS OF TREATMENT FROM THE PUBLIC HEALTH STANDPOINT

The benefits of massive dose chemotherapy may be discussed with regard, first, to the public health aspects and, second, from the standpoint of the individual patient

With massive dose chemotherapy, the patient is institutionalized for seven days and receives active treatment for five days. No institutionalization is required for routine therapy.

With massive dose chemotherapy, no ambulatory treatment is required other than for follow-up purposes. Routine treatment means weekly visits at a highly organized clinic.

The infectivity of the patient under routine therapy is three weeks, during which time he mingles with the community. Our patients are dark field negative by the end of forty-eight hours in the hospital. At no time after their discharge do they menace their contacts.

One hundred per cent of our patients complete treatment. If they are lost from follow-up they have exactly the same chance for a satisfactory result as those who have been faithful. In routine therapy, The Cooperative Clinical Group,⁴¹ reporting under the auspices of the United States Public Health Service, state that in their six clinics, including that of Johns Hopkins Hospital from which Moore reports, there was an 84 per cent case loss. Stated positively, sixteen patients in one hundred receive what the group believes to be adequate treatment.

THE RESULTS IN TERMS OF THE INDIVIDUAL PATIENT

The results of massive dose arsenotherapy from the standpoint of the individual patient have been reported, under the auspices of the distinguished Committee that has supervised the work.

The first series of twenty-five patients receiving neoarsphenamine was treated at The Mt Sinai Hospital on the Services of George Baehr in 1933. The immediate results appeared in 1935 and the five-year results in 1939.

The second neoarsphenamine series, now under the direction of the Committee, is approaching a span of observation averaging three years.

The third series of patients received Mapharsen in insufficient dosage. At first 400 mgm were employed. Tentatively and cautiously, the dosage was worked up to 1200 mgm, the amount that is now considered optimal. An average of 700 mgm of Mapharsen was given in this series. Series three has been followed for approximately eighteen months.

The fourth group of patients received 1200 mgm of Mapharsen. The results of therapy in this category are to be compared with the results in the neoarsphenamine series. The results are still incomplete, since the last patient was treated less than six months ago. I am at liberty today to discuss only those results published by our Committee as read at the meeting held at The Mt Sinai Hospital, in April, 1940.

RE-TREATMENT

In none of the four series was any adjuvant treatment with bismuth or mercury administered. This was not done because of lack of confidence in these drugs. Their administration was omitted in order that a relatively pure clinical experiment might be conducted. In the neoarsphenamine series the patients were not re-treated. It was understood that the results would stand or fall on the basis of the single course. In the small-dose Mapharsen series it soon became obvious that our original dosage was insufficient. Rather than sacrifice the welfare of the patient to the experiment, the policy of re-treatment was instituted. Approximately 10 per cent in this group required second courses. In the large dose Mapharsen series the number of re-treatments has been reduced to 4 per cent. Several of the patients who picked up fresh infections were also re-treated by massive dose arsenotherapy.

Patients who were re-treated were reclassified according to their individual progress.

THE CLINICAL RESULTS OF MASSIVE DOSE ARSENOTHERAPY

The clinical results are reported in four groups: (1) Patients who were *lost* from observation, (2) those whose reports might be *pending* or *incomplete*, (3) unqualified *failure*, and (4) *satisfactory*. The word "cure" has never been used in any report.

Loss The case loss in all three groups is 10 per cent. Each of these patients completed treatment. Each has a chance for successful outcome equal to that of those faithful in the follow-up. Since the records are inadequate, the percentage figures noted below exclude the lost cases. In making comparisons with patients treated in routine fashion, it must again be recalled that the Cooperative Clinical Group has a case loss of 84 per cent, none of whom received what is regarded as an adequate amount of therapy.

Pending In each of our groups, certain patients have been classified

as pending since their records are incomplete. There are 4 per cent in the neoarsphenamine series, 6 per cent in the small dose Mapharsen series, and 21 per cent in the more recent Mapharsen group, many of whose records are soon to be completed satisfactorily.

FAILURE

Unqualified failures have occurred in all three groups. These patients have had either (1) an infectious relapse at the site of the chancre, or (2), without clinical symptomatology, they exhibited serum fastness, or (3), serologic relapse. Late syphilis of the central nervous system or the cardiovascular apparatus has yet to be seen. Any lesion other than that at the site of the original sore has not been observed.

Spinal fluid examinations have been made almost without exception. There was but one positive test, and that in a morphine addict with a syphilitic wife.

SATISFACTORY RESULT

A satisfactory clinical result is reported in patients who have no clinical symptoms and who have repeatedly and persistently negative serologic reactions by the Wassermann, Kolmer, Kline and Kahn techniques. This has been the outcome in 91 per cent of the neoarsphenamine group, 86 per cent of the small dose Mapharsen group (with 6 per cent still pending) and 78 per cent of the large dose Mapharsen group (with 21 per cent still pending). Nineteen patients were re-treated when their progress appeared unsatisfactory at the crucial period between the tenth and sixteenth week. Fifteen were in the small dose series, and but four in the optimum dose group. Following the second courses, the results could be reclassified as satisfactory.

In the analysis of the satisfactory group, it is particularly to be noted that it contained almost every patient whose infection was of a duration of eight weeks or less. The unsuccessfully treated patients were recruited entirely from those whose infection was of a duration of more than eight weeks.

COMPARISON WITH RESULTS OF ROUTINE THERAPY

What are the results of routine therapy in comparable cases? The figures to be presented make difficult any satisfactory comparison. Firstly, those presented by the Cooperative Clinical Group are from series in

which there is an acknowledged 84 per cent case loss. It is not stated whether the published statistics are based on the number of patients who instituted therapy or those that received adequate therapy. If it is on the basis of those who instituted therapy, and 84 per cent were lost, then only 16 per cent can possibly have had a satisfactory result if every one was cured. On the other hand, if the figures are given as the results in those patients who successfully completed therapy, then comparison with our results is unfair since 100 per cent of our patients completed therapy whether or not they were followed.

Mindful of these possible errors in calculation, four sets of routine figures will be given.

Moore reports, in 1423 patients with early syphilis, that he had 8 per cent failure, and 92 per cent serologic reversal. In his text book³⁶ he reports on a second group, comparable with ours, with primary sero-negative, primary sero-positive and early secondary syphilis. There were 52 per cent who became serologically cleared and 48 per cent whose course was unfavorable.

Stokes,³⁷ treating 606 patients by continuous treatment, had 86.8 per cent clearing and 13.2 per cent unfavorable. In a second series of 306 patients, with partly continuous and partly intermittent treatment, there was clearing in 59.4 per cent and 40.6 per cent unfavorable.

The individual results of massive dose arsenotherapy in early syphilis, as compared with those obtained in routine therapy, may conservatively be said to equal the best reported, and far transcend those following less than optimal therapy under less than optimal conditions. If the comparison could be made on the basis of the results in consecutive series of patients initiating therapy, it is highly probable that the satisfactory results in massive dose arsenotherapy would so far exceed those obtained in routine therapy as to outweigh all other considerations, even those voiced by the most captious.

CONCLUSIONS

Intravenous drip chemotherapy provides for the direct delivery of relatively massive doses of potent therapeutic agents such as the sulfonamides and the arsenicals. By this means effective concentrations may be produced and maintained without the hazard of the immediate toxic phenomena of "speed shock." Contrary to the expectancy, there do not appear late toxic complications resulting from excessive dosage.

or cumulation. Difficulties due to idiosyncrasy crop up unexpectedly, causing treatment morbidity and treatment mortality. The incidence of these closely approximates those of routine therapy. The results of therapy approach the goal of the chemotherapist. They would seem to justify the hazards of increased toxicology, were these present. Richer and wider experience with intravenous drip chemotherapy, using other available preparations in diverse clinical infections, should offer greater hope and a broader horizon in the struggle for the relief of human suffering.

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PROCEEDINGS OF ACADEMY MEETINGS

STATLED MEETINGS

NOVEMBER 7—*The New York Academy of Medicine* Executive Session—a) Reading of the minutes, b) Report of Nominating Committee ¶ Papers of the evening—New knowledge of vitamins B and K—a) Vitamin B complex, Norman Jolliffe, Associate Professor of Medicine, New York University College of Medicine, b) Vitamin K, William DeWitt Andrus, Associate Professor of Surgery, Cornell University Medical College ¶ Report on election of Fellows

NOVEMBER 28—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The Second Harvey Lecture, "Thrombosis and the Action of Heparin," Charles H. Best, Professor of Physiology, University of Toronto

DECEMBER 5—*The New York Academy of Medicine* Executive session—a) Reading of the minutes, b) Report of Nominating Committee, c) Election of Academy officers ¶ Papers of the evening—Newer knowledge of liver disease—a) Surgical aspects, I. S. Ravdin, George Lieb Harrison Professor of Surgery, University of Pennsylvania, School of Medicine, b) Evaluation of laboratory methods, Alexander B. Gutman, Assistant Physician, Presbyterian Hospital, c) Clinical methods, Franklin M. Hanger, Associate Physician, Presbyterian Hospital ¶ Report on election of Fellows

DECEMBER 19—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The Third Harvey Lecture, "The Electrolytes of Tissues and Body Fluids," A. Baird Hastings, Professor of Biological Chemistry, Harvard Medical School

SECTION MEETINGS

NOVEMBER 1—*Surgery* Reading of the minutes ¶ Presentation of cases—a) Case

report of bilateral ligation of internal and external carotid arteries for cerebral arteriovenous aneurysm, Bronson S. Ray, b) Five cases of osteomyelitis of the cranial vault, Joseph E. J. King, Discussion by Frederick M. Law ¶ Papers of the evening—a) Myeloscapy Endoscopic diagnosis of conditions affecting the cauda equina and lower spinal cord, James Lawrence Pool (by invitation), b) Surgical treatment of paralysis agitans (moving picture illustrations), Tracy J. Putnam ¶ General discussion ¶ Executive session

NOVEMBER 6—*Dermatology and Syphilology* Presentation of cases—a) Mt. Sinai Hospital, b) Miscellaneous cases ¶—a) Eulogium—Wm. A. Pusey, Howard Fox, b) Eulogium—Ludwig Oulmann, Herman Goodman ¶ General discussion ¶ Executive session

NOVEMBER 12—*Combined Meeting, Section of Neurology and Psychiatry and the New York Neurological Society* Reading of the minutes ¶ Presentation of case—a) Amyotrophic lateral sclerosis treated with synthetic vitamin E, I. S. Wechsler ¶ Papers of the evening—a) Changes in cerebral blood-flow and arterio-venous oxygen difference during insulin hypoglycemia, H. E. Himwich (by invitation), K. M. Bowman, C. Daly (by invitation), Mr. J. F. Farekas (by invitation), J. Wortis (by invitation), W. Goldfarb (by invitation), Discussion by Tracy J. Putnam, Ephraim Shorr, b) Studies on pain, nature of pain due to local cooling and the mechanism of its production, Stewart G. Wolf (by invitation), J. D. Hardy, Ph.D. (by invitation), Discussion by Harold Wolff, William Bierman ¶ General discussion

NOVEMBER 13—*Historical and Cultural Medicine* Reading of the minutes ¶ Papers of the evening—a) The evolution of clinical sphygmomanometry, William Hall Lewis, Jr., Discussion by Lewis

For Frissell, Charles J Brin (by invitation), Edward H Hume, b] Illustrious figures in Chinese medicine, Edward Hicks Hume, Discussion by Professor Cyrus H Peake (by invitation) ¶ General discussion

NOVEMBER 14—*Pediatrics* Residents' program Reading of the minutes ¶ Papers of the evening—a] New York Hospital, Endocarditis due to a fusiform bacillus, Martin J Glynn (by invitation), Discussion, Samuel Z Levine, b] New York Post-Graduate Medical School and Hospital, Sick cell anemia in a white family, Francis C DeLorenzo (by invitation), Discussion, Marshall C Pease, c] Long Island College of Medicine, Erythroblastosis fetalis in dissimilar twins associated with a severe maternal anemia and hypoproteinemia, Peter A Perillo (by invitation), d] Harlem Hospital, Parke-Weber-Dimitri disease (cerebral telangiectasis), Maurice M Kay (by invitation), e] Babies' Hospital, Acute episodes in glycogen disease, Richard G Hodges (by invitation), Discussion by Howard H Mason, f] Flower and Fifth Avenue Hospitals, An undiagnosed case with a septic temperature of six months duration and a bizarre clinical picture, Sidney H Gurian (by invitation) g] Lincoln Hospital, Staphylococcus septicemia with recovery in a three-year-old child, Edward Press (by invitation), Discussion by Harry S Altman, h] Mount Sinai Hospital, Pneumococcus meningitis recovery in an infant aged ten months, Arnold Widerman (by invitation), Discussion by Bela Schick

Orthopedic Surgery—Instead of the regular meeting at the Academy of Medicine, the Section of Orthopedic Surgery met on November 15 with the Philadelphia Orthopedic Club in Philadelphia

NOVEMBER 18—*Ophthalmology* Exhibits—a] Comparative anatomy of the eye, Army Medical Museum, Lt Col J E Ash, Washington, D C (by invitation), b] Stereoscopic drawings of ophthalmologic neuro-anatomy, P J Ienfelder, Lee Allen, Iowa City, Iowa (by invitation),

c] Mammalian fundi, LeGrand Hardy, d] Normal variations of the optic canals, Raymond L Pfeifer ¶ Reading of the minutes ¶ In memoriam—Dr Ben Witt Key, Samuel Oast ¶ Papers of the evening—The clinical aspects of anatomy, a] The orbit, Raymond N Berke, Hackensack (by invitation), b] The central nervous system with particular regard to the visual pathway and the oculo-motor system, George A Blakeslee, c] The eyeball, F Bruce Fraleigh, Ann Arbor (by invitation) ¶ General discussion

NOVEMBER 19—*Medicine* Reading of the minutes ¶ Papers of the evening—a] Medical approach to the cancer problem, Cornelius P Rhoads, b] Diagnosis and treatment of diseases of the lymph nodes, Francis Carter Wood, Discussion by James Ewing ¶ General discussion ¶ Executive session

NOVEMBER 20—*Otolaryngology* Reading of the minutes ¶ Papers of the evening—a] Surgical aspects of carcinoma of the larynx, John D Kernan, b] Roentgenotherapy of cancer of the larynx and pharynx, Maurice Lenz ¶ General discussion

NOVEMBER 20—*Genito-Urinary Surgery* Reading of the minutes ¶ Papers of the evening—Symposium on the management of genito-urinary malignancies—a] Malignancies of the prostate, Lloyd Lewis, Johns Hopkins University, Baltimore (by invitation), b] Malignancies of the urinary bladder, Ernest M Watson, Buffalo (by invitation), c] Malignancies of the kidney, Henry G Bugbee ¶ Discussion opened by—a] Roy B Henline, b] Nathaniel P Rathbun, c] Fedor L Senger ¶ General discussion ¶ Executive session

NOVEMBER 26—*Obstetrics and Gynecology* Reading of the minutes ¶ Papers of the evening—Program by the Living-in Department of New York Hospital ¶ Physiology of pregnancy—a] Hormones, Herbert F Traut, b] Vitamins, Carl T Javert (by invitation) c] Urinary tract, Charles M McLane (by invitation)

d] Metabolism, A T Milhorat (by invitation), e] Diet, R Gordon Douglas (by invitation), Ralph C Benson (by invitation), Discussion by Alfred C Beck

DECEMBER 3—*Dermatology and Syphilology*
Presentation of cases—a] New York University College of Medicine and Bellevue Hospital, b] Miscellaneous cases
¶ Discussion of cases ¶ Executive session

DECEMBER 6—*Surgery* Reading of the minutes ¶ Presentation of cases—a] From the Babies Hospital—1 Diaphragmatic hernia, 2 Ligation of patent ductus arteriosus (3 cases), 3 Bleeding Meckel's diverticulum, 4 Gangrenous intussusception, Discussion by E J Donovan, b] Case illustrating paper of evening, Percy Klingenstein ¶ Papers of the evening—a] Meckel's diverticulum in infancy and childhood, Percy Klingenstein, Discussion by Edward H Peterson, b] Acute abdominal conditions in children, Charles W Lester, Discussion by Charles E Farr ¶ General Discussion

DECEMBER 10—*Neurology and Psychiatry*
Reading of the minutes ¶ Papers of the evening—a] Spontaneous occlusion of the common carotid artery, Morton Galdston (by invitation) Sidney Govons (by invitation), S Bernard Wortis, Discussion by J Murray Steele, Henry K Taylor, b] Further results of vitamin B₆ therapy in paralysis agitans, Norman Jolliffe, Discussion by Josephine Neal, c] Electro-encephalographic changes during hyper-ventilation in epileptic and non-epileptic disorders, Norman Q Brill (by invitation), Herta Seidemann (by invitation), Discussion by Richard M Brickner, Paul F A Hoefer (by invitation), d] The human electrocorticogram A study of electrical potentials taken directly from the exposed brain in health and in disease, John E Scarff, Mr Walter F Rahm (by invitation) Discussion by Tracy J Putnam, S Eugene Barrera (by invitation)

DECEMBER 12—*Pediatrics* Reading of the minutes ¶ Papers of the evening—a] Emphysema A dominant finding in an acute respiratory infection, Margaret R Reynolds, Discussion by Marshall C Pease, b] So-called essential hypertension in childhood, Irwin Philip Sobel, Discussion by Maurice Bruger (by invitation), Henry A Schroeder (by invitation), John D Little, c] The normal development of the male genitalia and secondary sex characteristics from birth through puberty, William A Schonfeld (by invitation), Discussion by Hilde Bruch (by invitation), Harry H Gordon (by invitation) ¶ Showing of film—"When Bobby goes to school"

DECEMBER 16—*Ophthalmology* Demonstration of cases ¶ Exhibits of new ophthalmological instruments by various firms ¶ Reading of the minutes ¶ Presentation of cases—a] A case of intra-epithelial epithelioma of the cornea, John S McGavie (by invitation), b] A case of lattice keratitis, W Guernsey Fretz, Jr, c] A case of symmetrical bilateral coloboma of the iris, lens, retina, and choroid, Martin H Kilmann (by invitation), d] A case of cystic pterygium operated successfully by a new technique, William B Doherty, e] Three cases of episcleritis in rheumatoid arthritis, Jules W Smoleroff (by invitation), f] A case of malignant teratoma of the orbit, Albert V Saradarian (by invitation), g] A case of Boeck's sarcoid, Jesse M Levitt (by invitation) ¶ Papers of the evening—a] Capsulotomy and iridocapsulotomy technique with a special keratome and iridocapsulotomy scissors, Conrad Berens b] The mechanics of optic nerve traction upon the retina during ocular rotation, with special reference to retinal detachment, Benjamin Friedman

DECEMBER 17—*Medicine* Reading of the minutes ¶ Presentation of cases—a] Measurement of the pain threshold, a new approach to the study of pain, James D Hardy (by invitation), b] Measurement of the pain threshold, the effect of analgesics, Harold G Wolff Discussion by McKeen Cattell, Harry Gold, c] The

significance of muscular weakness in Graves disease (with moving pictures), Ephraim Shorr (by invitation), Discussion by Ade T. Milhorit (by invitation) ¶ General discussion ¶ Executive session

DECEMBER 17—*Obstetrics and Gynecology* Reading of the minutes ¶ Papers of the evening—a] The pulse and respiratory rate during labor, Curtis I. Mendelson (by invitation), Discussion by Harold E. B. Pardee, b] Cause and prevention of transfusion accidents in pregnancy, Philip Levine, Eugene M. Katzen. Discussion by Reuben Ottenberg, Iman Burnham (by invitation)

DECEMBER 18—*Otolaryngology* Reading of the minutes ¶ Reports of cases—a] Hemangioma of the nasal cavity with persistent, severe hemorrhage, cured by radium therapy, Samuel Morse (by invitation), Discussion by W. Wallace Morrison, b] Type III pneumococcus meningitis and septicemia with complete recovery, M. Moghtader (by invitation) ¶ Papers of the evening—a] Sulfamylamide in otitis media in children, Edwin Bilchick, George H. O'Kane (by invitation), b] Fossilectomy with conservation of tissues, fascia and mucosa, Robert H. Fowler

DECEMBER 18—*Genito-Urinary Surgery* Reading of the minutes ¶ Papers of the evening—Symposium on non-specific infections of the genito-urinary tract (excluding gonorrhea and tuberculosis)—a] Chemotherapy in urinary tract infections, Edwin P. Alvey, Durham, North Carolina (by invitation), b] The formation of urinary calculi produced by the *Proteus ammoniae*, C. Donald Creery, Minneapolis (by invitation) ¶ Discussion by Meredith Campbell ¶ General discussion ¶ Executive session

DECEMBER 20—*Orthopedic Surgery* Reading of the minutes ¶ Presentation of cases—a] Fracture through sacroiliac joint associated with nerve injury. End-result following muscle transplantation, Ernest

Burgess (by invitation) b] Fracture of the acetabulum followed by limitation of motion of the hip. Acetabuloplasty, Donald Starr (by invitation) ¶ Paper of the evening—Fracture of the pelvis. Anatomical reduction and treatment of complications, F. Walter Carruthers. Little Rock, Arkansas (by invitation) ¶ General discussion by John A. Taylor, Ralph I. Barrett, Samuel A. Jahss (by invitation)

1 F F I L I A T T E D S O C I E T I E S

NOVEMBER 18—*New York Roentgen Society* (in affiliation with The New York Academy of Medicine) Papers of the evening—a] The effect of the shape of the heart on the electrocardiographic pattern, Arthur M. Master (by invitation), b] Contrast visualization of the cardiac chambers in emphysema, Mary L. Sussman, Morris F. Steinberg (by invitation), Arthur Grishman (by invitation) c] Constructive pericarditis—1. Circulatory dynamics, William M. Hitzig (by invitation), 2. Clinical and roentgen features, Bernard S. Oppenheimer (by invitation), 3. Surgical aspects, Harold Neuhof (by invitation) ¶ Discussion—a] Charles Aden Pindexter (by invitation), b] George P. Robb (by invitation), c] Samuel Olcott Thompson (by invitation) ¶ Executive session

NOVEMBER 28—*New York Pathological Society* (in affiliation with The New York Academy of Medicine) Case report—a] Postpartum necrosis of the pituitary gland, Alfred Plaut, Beth Israel Hospital ¶ Papers of the evening—a] An experimental study of nutrition and age as factors in the pathogenesis of common diseases of the rat, John A. Saxton, Jr. (by invitation), Cornell University Medical College, b] Relationship of bacteriological procedures to the diagnosis and therapy of pneumonia, Wheelan D. Sutliff (by invitation), Bureau of Laboratories, Department of Health ¶ Executive session

DECEMBER 16—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) Symposium on arthritis—a] Classification and clinical aspects, Currier McEwen (by invitation), b] Pathological aspects, D Murray Angewine (by invitation), c] Radiological aspects, Haig H Kasabach ¶ Discussion by Edward F Hartung (by invitation), Ralph H Boots (by invitation)

DECEMBER 18—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) Case Reports—

a] Spontaneous non-traumatic rupture of posterior papillary muscle of the heart, Caspar Burn, Kings County Hospital, b] Carcinoma of the stomach with skeletal metastases, myelophthisic anemia and splenomegaly, M W Johannsen, Bellevue Hospital ¶ Papers of the evening—a] Concerning the etiology of cystic fibrosis of the pancreas, Henry Brody, Beth Israel Hospital, b] Phosphatase in normal and malignant tissues, Jacob Furth, E A Kabat (by invitation), Cornell University Medical College ¶ Executive session

DEATHS OF FELLOWS

HARTWELL, JOHN AUGUSTUS 1067 Fifth Avenue, New York City, born in Deckerstown, County Sussex, New Jersey, September 27, 1869, died in Oakdale, Long Island, New York, November 30, 1940, received the degree of Bachelor of Philosophy from Yale University in 1889 and graduated in medicine from Yale Medical School in 1892, elected a Fellow of the Academy November 7, 1901 served as a member of the Committee on Public Health Relations 1917-1929, as vice-president of the Academy 1918-1920, as president 1929-1932, as a member of the Committee on Medical Education 1933-1934, and as a member of the Board of Trustees in 1928, 1933-1934, and

again from 1939 until his death. He was director of the Academy 1934-1939.

Dr Hartwell was emeritus clinical professor of surgery at Cornell University Medical College and was consulting surgeon to Bellevue, Presbyterian, Reconstruction Unit of Post-Graduate, Memorial and Lincoln Hospitals, the Lawrence Hospital in Bronxville, the United Hospital in Port Chester and the New York Infirmary for Women and Children. In 1939 he became associate director of the American Society for the Control of Cancer.

He was a Fellow of the American College of Surgeons and a member of the New York Surgical Society, the American Surgical Association, the Society of Clinical Surgeons, the American Association for Thoracic Surgery, the American Medical Association and the County and State Medical Societies.

During the World War, Dr Hartwell served in the Army Medical Corps and was discharged with the rank of Major.



JOHN A. HARTWELL

1869-1940

IN MEMORIAM

JOHN A. HARTWELL

In the death of our Ex-President and Ex-Director, John A. Hartwell, the Academy has suffered a very great loss. Captain Liddell Hart in his 'Reputations Ten Years After' says of General Gallieni, the real author of the Miracle of the Marne "but the finest epitaph and that most acceptable surely to him, is also the simplest 'Gallieni —la tête haute'." How descriptive of Hartwell! I can imagine no truer motto for him throughout his whole career in athletics, teaching, surgery, and his later executive positions.

My acquaintance with him began as an undergraduate at college where one of my early memories of him is his futile but game pursuit of Lee, who scored a winning touch-down in a Yale-Harvard game. As captain of the famous '92 Crew, which made in June the second fastest record time at New London, he displayed his courage, a dominant trait throughout his life, in the removal against the advice of the coach of a famous powerful, but overweight member of the crew who had also rowed the year before but could not pull his own weight in the boat. Whatever the odds, once his mind was made up that a course of action was desirable 'Josh' fought indomitably, sometimes with steam-roller methods, to accomplish his purpose. And he was usually right! Another early recollection is in Professor Chittenden's laboratory, Sheffield Scientific School. I was puzzled in some mathematical calculation when Chittenden finally remarked impatiently 'Josh Hartwell would never have done this, but then he was bright!'

In looking over Dr. Hartwell's vast number of professional appointments, both teaching and hospital, it is difficult to know which to emphasize. Shortly after graduation as intern he became Instructor and in 1901 Assistant Professor of Physiology at Cornell and then as natural in one who had come

through Chittenden's laboratory, did much research work. His experiments in high intestinal obstruction in dogs and the prolongation of life by large parenteral doses of normal saline is fundamental, and has become the basis of subsequent treatment in humans. On the academic side, in the various grades of Assistant Professor of Surgery, Associate Professor of Surgery, Professor of Clinical Surgery and Professor Emeritus of Surgery at Cornell from 1909 to 1936, he threw the same energy into the instruction of medical youth that distinguished him in his own hospital and private practice. His main hospital interests were at Bellevue to which he became attached in 1903, rising through various grades until in 1916 he became Visiting Surgeon and Director of the 2nd Division and finally Consultant in 1928. Into all this work Dr. Hartwell again threw all of his energy and it was in this period that he organized the Cornell Clinic where patients of moderate means received expert care for a small fee. No one of his appointments gave him more pleasure than his nomination in 1908 to the post of Assistant Surgeon at Presbyterian Hospital, where he had interned. Well do I remember the dinner given at the University Club on this occasion and Josh's delight. This connection lasted until the union of Columbia and Presbyterian Hospital and the consequent withdrawal of the Cornell members from the staff. In all of his hospital and teaching appointments he had something of the attitude which later characterized him in his executive positions, the courage to fight for what he considered right, regardless of opposition. This was ably satirized by Dr. Corwin in his speech at the Academy Dinner on Dr. Hartwell's retirement from the Directorship which described him as a mixture of Don Quixote and Cato. Yet throughout his speech this truth was emphasized: he was essentially a crusader with all the virtues and

ices characteristic of that type of mind. This, however, was qualified by a rare judgment of men and a diplomacy which enabled him to use even those who disagreed with him on details.

During the war he held the rank of major and taught war surgery to surgeons entering the army and was instrumental in standardizing surgical dressings used in the army. In France in 1918-19 he was assigned to duty with the Chief Surgeon of the First Army.

His association with the Academy began with his election as fellow in 1901. He served on the Public Health Committee from 1917 to 1929 and at this time began his acquaintance with public health problems which later, in his Presidency and Directorate, gave him the knowledge to speak with authority before civic and legislative boards. This he did convincingly on many occasions, becoming widely known as the civic, state and, to a lesser extent national, mouthpiece of medical opinion. Here he struck a mean between the extreme liberal and extreme conservative positions. He was particularly interested in the fight against cancer and in 1939 became Associate Director of the American Society for the Control of Cancer. He made frequent appearances before legislative committees in Albany to protest against the enactment of legislation which would prohibit experiments on living dogs. He was a determined opponent of fee-splitting and also directed attention to the dangers of overspecialization and urged that there be more physicians of the

type of old-fashioned family doctor who was skilled in all branches of medicine and specialized in none.

As Director of the Academy of Medicine he was faced with the problem of declining revenue and the necessity, in the eyes of many of his associates, of balancing the budget. Full of optimism, which with his invincible courage was perhaps one of his two most distinguishing characteristics, he declined to cut down any of the Academy's activities, insisting that appeals to the public could balance the budget and it was unthinkable that the Academy should curtail any of its Public Health, Medical Education, or Medical Information work. During all of his later years he was crippled much of the time by vascular trouble of the legs, which had plagued him ever since an attack of typhoid phlebitis during his hospital internship. Directing the affairs of the Academy from a hospital bed, or from his oscillating table, and being carried on a stretcher to vote or to a duck blind, he seems here to be carrying out to the full the motto, "La Tete Haute."

Always an ardent sportsman, he was a member of the Board of Directors of "More Game Birds in America" and it was his expressed hope that he might die with a fishing rod or a gun in his hand. In the end death came as his guide handed him his gun on his last duck-shoot.

LEWIS FOX FRISSELL

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED
IN THEIR CONTRIBUTIONS

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1941

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MARCH 1941

INAUGURAL ADDRESS OF THE PRESIDENT OF
THE NEW YORK ACADEMY OF MEDICINE*

MALCOLM GOODRIDGE

WHAT IS THE NEW YORK ACADEMY OF MEDICINE?

FIRST, let me express my appreciation of the great honor which has been conferred upon me by the Fellows of The New York Academy of Medicine, in re-electing me their President

Two years ago, I avowed a full understanding of my responsibility. My responsibility continues, it has even increased in the two years in which I have been in office, and, while I may not have the same awareness today of my inadequacy that I had then, my humility is undiminished and my enthusiasm has progressed. Perhaps this is a happy combination, humility and enthusiasm.

I have been impressed, during my two years in office, by the fact that the public knows really little of what the Academy is, and what its accomplishments have been.

Why should this be so? In searching for the reason, I have concluded that it is chiefly because we, as individual physicians who form the Fellowship of the Academy, have an obsession against advertising, it is a traditional violation of medical ethics to advertise, and we have

* Given January 2, 1941 at the Annual Meeting of The New York Academy of Medicine

carried this aversion into our administration of the Academy

I feel that this is a mistaken philosophy, I am sure it is wise, even necessary, for the public to know what we are doing

Two years ago, I told something of the history of the Academy. Tonight, I am going to try to tell you what the Academy is

After all, what is The New York Academy of Medicine? It might be defined as an association of physicians, incorporated under the laws of the State of New York, June 23, 1851, for the purpose of promoting the advancement of medical science by such means as to them shall appear expedient and proper, and now occupying the premises at 2 East 103d Street, and, even if I went no farther than that, it would be news to *most* people

To begin with, I should say there is a general misunderstanding concerning the relationship of the Academy to organized medicine. There is really *no* relationship, except insofar as individual Fellows of the Academy are members of the medical societies in the county, state, and country which make up organized medicine. We as individuals are vitally interested in the affairs of the physician, in his training and ethics, in his relationship to the public, and in his economic welfare.

The other day, I reread the Inaugural Address of a past President of the Academy who is still living, Dr. Samuel W. Lambert. He said, "The New York Academy of Medicine is not a local medical group. It has become a national institution." And, with rare foresight and vision, he said of our new building, "This building is an asset of which we may be proud, but it is also a liability which calls for increased expenditures now and in the future. No one must forget that the future will always call for increasing endowments to meet the necessary expenses of the present work and also expand into the unknown and compelling activities of the future. This academy, like every educational institution, must go on to new fields of work or retrograde and slip from its position of prominence." This address of Dr. Lambert's was delivered in 1927, a short time after we moved out of our old building on West 43rd Street, where the Academy was in large measure self-sustaining and supported by membership dues.

Curiously enough, one of the difficulties in which we now find ourselves is due, in part at least, to the financial support of the Foundations which endowed us with large sums of money, stimulating us to go forward with projects we had not previously undertaken. The de-

mands on us increased in direct proportion to the service we rendered, that is, as we improved our service, the demands grew. With the aid of the Foundations, we have come this far.

Let me review briefly for you what the several departments of the Academy of Medicine have done and are doing. Please remember, I cannot in the short time available this evening tell the whole story of our Library and of the Standing Committees of the Academy, nor, in discussing the various committees shall I make any attempt to arrange them in the order of their importance. I am convinced this could not be done under any circumstances, for, with the Library as the hub, each department is a spoke in the wheel, of equal strength, and moving with equal velocity in any given direction.

Do you know that our Library is regarded by the Public Library of New York as the natural repository of medical books, and that it is particularly rich in books on medical biography and the history of medicine? And do you know that in 1939 the Academy Library served more than six times as many readers as any other medical library in the country, and that of these readers *eighty-seven per cent* were *not* Fellows of the Academy?

Do you know that in 1939, through our interlibrary loan service, we loaned 3,040 volumes to 156 libraries, at an actual cost to the Academy of \$1,520, while the books borrowed by the Academy for the use of its Fellows totaled but seven volumes, at a cost of three dollars and a half?

Do you know that the bibliographical service furnished by our Library is one of but three such medical services in this country, and that the charges for this service do not nearly cover the cost? This, of course, represents a valid contribution to medical scholarship.

Do you know we have a card index to our Library Portrait Catalogue, with some 47,000 cards, representing 86,000 portraits of 30,000 individuals? This list is in constant use, and the Catalogue is unique in medical library service. Reproduction of library material by photograph, photostat, and microfilm served 1,381 clients in 1939.

Do you know what the Union List of Serials is? It contains the periodical holdings of hundreds of libraries in the United States and Canada, and up to 1925 it contained 75,000 entries. Since 1930, there has been an annual supplement, published quarterly. The cost of the original list was \$70,000, of which the Academy paid \$1,800, in addi-

tion to the cost, \$2,850, of listing its holdings, and we contribute about \$500 a year toward meeting the cost of the annual supplement Obviously, a list of this kind has immense value as a reference book to the entire medical world

Do you know that our Library has given duplicates to libraries in other countries, to Japan, in 1924, to replace losses suffered in the earthquake, to China, from 1932 to 1940, to replace losses due to the Japanese invasions, to Hungary, to Fiji, and to Chile? Do you know that in 1939, through the Exchange Service of the Medical Library Association, we gave to 272 libraries in the United States and Canada 19,834 duplicates, and that the cost of handling this material was carried by the Academy, for the benefit of other libraries?

Do you know our Library has a collection of hospital and health reports, medical school announcements, and medical government documents from all over the world that is second to none?

And do you realize that these documents are costly to gather, to catalogue, and to store?

The Committee on Public Health Relations of the Academy is approaching its thirtieth birthday, having been in existence since 1911 Do you know that this Committee was entirely responsible for the transfer of quarantine of the Port of New York from the jurisdiction of the State to that of the Federal Government? And that it worked for the cleaning up and prevention of further pollution of the waters around the City of New York, that it made studies and recommendations to effect more efficient handling of city refuse, that it worked for improvement in housing conditions through recommendation of enactment of a new Tenement House Law in 1929, and for the correction of apparent maladjustments in the administration and application of the Workmen's Compensation Law, that it studied procedure in children's and domestic relations courts, with the result that the number of children brought before the bench has been reduced by half, that it worked for established standards for physical examination of factory workers from fourteen to sixteen years of age, and for periodic examination of school teachers, for improved conditions for school children in the matter of nutrition, schoolroom lighting and ventilation, and provisions for handicapped children, for better food and drug laws, and for the protection of the public from fraudulent advertising, that it initiated the movement for the establishment of a uniform nomenclature of dis-

ease, that it appointed a committee, back in 1927, to consider the need of a medical and public health museum, and today there has been established such a museum, the American Museum of Health, and that it has worked for the establishment of an Institute of Forensic Medicine? That studies as to clinical diagnosis for use in cardiac diseases, the control of venereal diseases and the disposition of carriers, and the care of mental defectives have been carried on by this Committee, and that it was asked to study the social and clinical aspects of marihuana poisoning, with the cooperation of the Departments of Health, Welfare, and Police? And that it has worked for more adequate hospital facilities for tuberculosis and contagious diseases? And that it participated in the study which resulted in an appreciable reduction in diarrheal deaths in the new born?

A subcommittee of the Public Health Relations Committee worked for a number of years, searching out the causes of maternal mortality and making recommendations which effected a reduction of 50 per cent of unnecessary deaths within five years after the publication of their report, six years ago. Do you know who the members of this subcommittee were? I doubt if many Fellows of the Academy could name them.

Do you know that as long ago as 1927, the Committee on Public Health Relations made certain recommendations to the Commissioner of Health, in order to safeguard the patient, the agency, and the professional donor, in the use of blood transfusion, and that these recommendations were adopted, placing agencies and professional donors under the control of the Department of Health, and that in 1930, under the motivating force of this same committee of the Academy, the Blood Transfusion Betterment Association was formed? And that this Association is now cooperating with the New York Chapter of the American Red Cross, in centralizing blood donors for the collection of blood plasma for wounded and shocked soldiers and civilians of Great Britain, and incidentally laying the foundation for the use of plasma in our own defense? Sacramento 2-8950, which you see frequently nowadays, associated with pleas for blood plasma for Britain, is the telephone number of the clearing house for plasma volunteers, and that clearing house is located on the fourth floor of this, our Academy building, in space contributed by the Academy for such use.

Bear in mind that one of the most important relationships of the

Academy to the public is the education of the doctor. How many of you ever stop to consider just how much the Committee on Medical Education does in this direction, arranging the scientific programs of the eight Stated Meetings which are held each year, arranging for twenty lectures given on Friday afternoons on subjects of current importance to physicians, and five lectures on Wednesday afternoons devoted to problems which the general practitioner is apt to encounter in the field of Obstetrics? And let me add that *all* of the Stated Meetings and the Wednesday Afternoon and Friday Afternoon Lectures are open to the entire medical profession.

Perhaps one of the most important functions of this Committee is the arrangement of the Graduate Fortnight, which is held in October of each year. During this Fortnight, a subject of live general medical interest is treated, and medical men from various cities, states, and countries enroll. The Fortnight consists of evening lectures by men from all parts of the country, recognized authorities in their particular fields, morning panel discussions, afternoon clinics in the various hospitals of this city, and a large exhibit of various items pertinent to the subject of the Fortnight. Last year, the subject was "Infections." The year before, it was "The Endocrines." Next October, it will be "Cardiovascular Diseases, including Hypertension."

The Committee maintains a Bureau of Clinical Information, concerning opportunities for medical instruction or education throughout the country, and publishes a daily bulletin of surgical operations in various clinics of the city, a daily bulletin of meetings, lectures, conferences, and hospital rounds, and a bulletin of clinical and pathological conferences and special rounds in the hospitals of New York.

It also cooperates with the Department of State of the United States, in guiding medical scientists and students from South American countries on their arrival in New York.

Separate from the Committee on Medical Education, but closely affiliated with it, The New York Academy of Medicine publishes a monthly medical journal called the Bulletin, under the authority of a duly appointed editorial board.

If you know that the Committee on Sections is a Standing Committee of the Academy, you are better informed than most, for some of the members of the Council did not know it until about a year ago, and yet, this is one of the most important features of our organization. The

chairman of this Committee is appointed by the Council from among the three Vice-Presidents of the Academy. There are eleven sections in all, ten scientific, each concerned with some special field of medicine, and one historical and cultural section. Each of these sections meets once a month, and various topics of importance in the medical world are discussed freely.

I would like to emphasize the fact that these Section meetings also are open to all members of the medical profession.

Finally, we have a Standing Committee known as the Committee on Medical Information, of very great importance, because it acts, as its name connotes, as a link between the entire field of medicine and the public.

Let me show you just how effective it is in this respect. The press has made a thousand inquiries, and there have been as many as two thousand from individuals, lay organizations, and commercial organizations within the last year. The answering of such inquiries has an extremely important bearing on the health of the community, and the work of this Committee is a feature of the Academy's work which the public knows almost nothing about. The people do not realize that they are being protected against misrepresentation in commercial advertising through the influence of this Academy activity.

Under the aegis of this Committee, a series of "Lectures to the Laity" is given every year, on topics of interest to the general public, which the Columbia University Press publishes in book form under the title, "The March of Medicine." The average attendance at the last series was 779.

A year ago, under a fellowship grant from the Rockefeller Foundation, the Committee made a study of radio broadcasting of medical information.

Under the direction of the Committee, a radio period, known as "Highways to Health," may be heard over Station WABC every week in the year.

The various committees of the Academy are bound together in a common interest. As evidence of this, let me cite an example. One of the most important of last year's conferences was held under the auspices of the Committee on Medical Information, the "Health Education Conference," which brought together public health officers, voluntary health organizations, and medicine, as such, on the one hand,

and the press and radio, chief distributors of news, on the other

The press of this city has drawn attention editorially many times to the part which The New York Academy of Medicine plays in the city's life, its friendship to the community, and its service to the public

The Library figures give us a fair index of Academy growth in all of its departments, since we moved, fifteen years ago, from 43rd Street into our present building. The total items in the Library, books, catalogues, pamphlets, periodicals, and theses, increased by 70 per cent, the readers using our Library increased during this same period of time by 185 per cent, while the Library personnel increased by but 60 per cent

In 1928, the Library expenditures were almost exactly the same as the budgetary allowance for the coming year

I fear I have burdened you with a dull story, told in facts and figures, but for some time it has been apparent to me that we must let the Fellows of the Academy and the public know what we are doing and what it costs to maintain this organization

I regret the lack of the gift of expression which would enable me to give you an idea of the enthusiasm with which the personnel of the Academy staff carries on in spite of some discouraging handicaps. I cannot find words which would adequately set forth my admiration for the devotion of the Fellows of the Academy who have given so much of their time, energy, and wisdom for the advancement of medical science and for the betterment of the public welfare

A year ago I called attention to the Academy deficit for the year ending December 31, 1939. Perhaps many of you do not yet know that a deficit of some eighteen thousand dollars in that year was met through the generosity of Mr. Bernard M. Baruch

During the past year the growth of the Library has been retarded and every department of the Academy has been shorthanded because your Budget Committee was compelled to make its allowance nearly forty-five thousand dollars less than the budgetary requests

Make no mistake about it, we are determined to go forward. We shall resist to the utmost any thought of turning back. But neither the fervor of the Fellows of the Academy nor its understaffed personnel can do it all. Unfortunately, we are not in a position to shoulder all of the financial responsibility for the future

If I have been in the least convincing, in relating my story of the Academy, its triumphs as well as its trials and tribulations, then I must

have demonstrated at the same time that we are worthy of liberal financial support

The Library needs more stack space. We own the ground on which an addition might be built for such use. The plans are drawn, not only for increase in the space required to house our books, but also for such rehabilitation of our present available space as will permit us to meet the tremendous increase in the demands which have been made on the Library in recent years.

A committee of Academy Fellows, under the chairmanship of Dr. Harold R. Mixsell, was formed early in the past year to raise the necessary funds to permit us to go forward and later to add to Academy endowment. A plan was adopted, under which we seek to raise \$550,000 immediately, for the structural changes in the Library which I have already mentioned and for greatly needed support of our annual budget. It is our hope that in five years we may in addition increase our endowment fund by \$1,250,000, so that there may be no interruption of Academy activities.

A suggestion made by Dr. Mixsell's committee, I am happy to announce, has become effective. A Lay Council or advisory committee has been formed as a permanent feature of the Academy organization. The following gentlemen have consented to serve in this Council: Messrs. Walter S. Gifford, Chairman, Arthur M. Anderson, George Blumenthal, Lewis H. Brown, Clinton H. Crane, Marshall Field, Joseph M. Hartfield, David M. Heyman, Philip W. Lennen, George W. Merck, and Edward L. Shea. They have met with Dr. Mixsell's committee individually and collectively, and have already rendered inestimable service in terms of helpful advice.

Let me say, in closing, that we have no delusions concerning our importance, and no illusions with regard to our accomplishments. What we have done in the past will give you some conception of what we are today. Our hope and ambition in matters concerning the public health and medical education are endless.

MEDICAL ASPECTS OF ARTERIAL
HYPERTENSION*

EDGAR V ALLEN

Division of Medicine Mayo Clinic Rochester, Minnesota

A DISCUSSION such as this should begin logically with a definition of what constitutes normal blood pressure, for unless we know the value for normal blood pressure we cannot know where normal blood pressure ends and hypertension begins. We cannot find out by averaging the blood pressure of a large group of patients. Statisticians are fond of pointing out that the average height of a population half of whom are 6 feet tall and half of whom are $5\frac{1}{2}$ feet tall is 5 feet and 9 inches. Yet there is not an individual in the group who has that height. Averaging blood pressures of a large group of patients will not allow us to conclude accurately what constitutes normal blood pressure. If one averages all of the figures, the figure for normal blood pressure will be too high and if one excludes frankly hypertensive values he is guilty of deciding beforehand the answer which he sought by such a study. Insurance figures do not help much either, for frequently the agent will not send to the insurance office the application of a candidate for insurance who appears to have hypertension. Also, the old rule that the normal systolic blood pressure is the age of the patient added to 100 is fallacious, for it is unquestionably true that the normal blood pressure of adults does not increase with age. The rather arbitrary upper limits of 140 mm of mercury for normal systolic blood pressure and 90 mm of mercury for normal diastolic blood pressure constitute a fairly adequate basis for determining normal blood pressure. However, recent studies of development of blood pressure and of survival of subjects whose blood pressures have been repeatedly observed indicate that the figure 140/90 is not the upper limit of normal blood pressure but indicates instead early hypertension. My associate, Hines,¹ has shown that in 70 per cent of patients who have blood pressures of 140/90 or slightly less, hypertension develops in twenty years, whereas

* Read October 3, 1940 before the Stated Meeting of The New York Academy of Medicine

A variation of this hypothesis is that overactivity of the sympathetic nervous system causes arteriolar constriction in the kidneys, inducing release from them of a chemical, vasoconstrictive substance which in turn results in widespread arteriolar constriction and hypertension. However, such substances have not yet been demonstrated in essential hypertension. Since the excellent work of Goldblatt³ and many others, there has been a tendency to assume that essential hypertension originates in the kidneys but there is no evidence, other than reasoning, that this is true. Most thoughtful students consider the cause of arteriolar constriction in hypertension to be uncertain at the present time.

It is now well known that hypertension of man indistinguishable from essential hypertension may be produced by unilateral renal lesions and that when a diseased kidney is removed surgically the blood pressure may return to normal. Barker and Walters⁴ have demonstrated this in an excellent manner. Unfortunately, such renal lesions are found very unusually in hypertension. While I do not have the exact figures, my impression is that a lesion of a kidney which is responsible for hypertension can be demonstrated less than once in 300 cases. Nevertheless, a thorough study of a patient with essential hypertension must include urographic examination, for occasionally we see a patient who has neither unusual blood cells in the urine nor a history suggesting infection or stone in the urinary tract but who has atrophic pyelonephritis to which hypertension is secondary. Interestingly, Hines and Lander⁵ have shown that hypertension seldom develops among patients who have atrophic pyelonephritis unless they had high normal blood pressures before pyelonephritis developed. This suggests that the substratum of hypertension must be present before pyelonephritis can provoke hypertension. It suggests also that pyelonephritis is only one of several specific stimuli which can cause hypertension. It is my impression that occasional demonstration of a renal cause for hypertension of man does not prove that all or most of essential hypertension is renal in origin but only that renal hypertension has been mistaken occasionally for essential hypertension.

One impressive feature of essential hypertension is the inheritance of it. It may seem strange that an individual can inherit a disease which does not become evident until middle adult life but there are examples of other conditions which occur similarly. Baldness, cerebellar atrophy, muscular dystrophies and atrophies may affect members of certain

families but not become apparent until after adolescence. Moreover, latent evidence of hypertension may be present early in life. Hines⁶ has shown that excessive responses of blood pressure to a standard stimulus occur in about 18 per cent of healthy school children who have normal blood pressure. This is approximately the incidence of hypertension among adults. There is yet only incomplete but none-the-less suggestive evidence that of all subjects with normal blood pressure hypertension develops only among those whose blood pressure increases excessively when a hand is immersed in ice water or as a result of some other standard stimulus. In other words, even in childhood there may be occult evidence of hypertension. Coming events cast their shadows before.

Almost 95 per cent of patients with hypertension have a family history of cardiovascular disease. Ayman's⁷ study shows that the incidence of elevated blood pressure in families in which both parents had normal blood pressure was only 3 per cent. If one parent had hypertension, the incidence of hypertension among the children was 28 per cent and when both parents had hypertension the respective figure was 45 per cent. The hereditary factor is well shown by the study of Hines,⁸ which indicates that the substratum of hypertension is inherited and is apparent before hypertension develops.

If the physician bears in mind that hypertension may result from a number of causes, he need not overlook a specific cause for elevation of the blood pressure. He must consider coarctation of the aorta, nephritis, obstruction to the free flow of urine, Cushing's syndrome, tumors of the suprarenal glands, the kidneys, or the ovaries, and pyelonephritis. However, these conditions are almost always obvious or very uncommon. There is actually little value, and only interest, in differentiating chronic nephritis with hypertension from essential hypertension with renal involvement. The great majority of cases of hypertension are of the essential type, and ordinarily differential diagnosis is not difficult or it is unimportant.

The importance of hypertension as a problem of health needs emphasis. High blood pressure is both a common disease and a serious one. Indeed, it appears to be more common and more deadly than cancer. At the Mayo Clinic, each year, we encounter from 5,000 to 6,000 patients who have definite hypertension. According to estimates of the Metropolitan Life Insurance Company cardiovascular-renal dis-

eases will kill 600,000 people in the United States in 1940 that is, they will kill four times as many people as cancer will. Apparently, hypertension accounts for from a half to three-fourths of all deaths referable to cardiovascular-renal disease, and thus is from two to three times as deadly as cancer. About a fourth of all deaths of individuals past fifty years of age is referable to hypertension.

The classification of essential hypertension is valuable in prognosis. Keith, Wagener and Barker⁹ have shown that the mortality in hypertension, groups 1 and 2, is 30 and 42 per cent, respectively, in four years from the time of their diagnosis, whereas, for a similar period, the mortality of hypertension, group 3, is 78 per cent and in group 4, it is 98 per cent. Among subjects who have systolic blood pressures of about 170 mm of mercury, the relation of actual mortality to expected mortality according to insurance statistics is as 219.6 to 100, among those patients whose systolic blood pressures exceed 200 mm of mercury, the actual mortality is to the expected as 827.5 is to 100. For individuals more than forty years of age, systolic blood pressure ranging from 35 to 44 mm in excess of normal increases the expected mortality two and a half times. Such a slight increase in blood pressure as that represented by the figures 170 to 174, systolic, and 106, diastolic, expressed in millimeters of mercury, increases the expected mortality two and a half times.

Many physicians appear to be misled by the observation that an occasional patient survives hypertension for many years. They may then believe that hypertension in general is not very serious. Such an attitude is wishful in part, for few physicians like to face the fact that there is no routinely effective treatment for hypertension. If the physician believes that hypertension is not a serious disease, failure to treat it satisfactorily will not be so disappointing as it will be if he realizes the importance of the condition. This belief in the benignity of hypertension neglects to take into account repeated observations such as those written in the preceding paragraph—namely, that hypertension usually is a serious disease which terminates the lives of those it afflicts within a relatively short span.

Another cause for concern is the apparently decreasing age at which hypertension endangers the lives of those who are afflicted with it. This is a clinical impression based on the repeated observations that hypertensive members of a third generation die earlier than hyperten-

sive members of the second generation of the same family, and that those of the second generation die earlier than those of the first generation, apparently all from hypertension. Not uncommonly on questioning, the physician finds a situation similar to the following: the grandfather died at seventy-two years of age of "stroke," the mother died at sixty of "Bright's disease" and the son, aged thirty-five years, is seriously ill from hypertension, which probably will terminate his life within a few months.¹⁰ It appears that the incidence of hypertension in the general population is increasing but the evidence is not conclusive. Among patients at the Mayo Clinic it increased from about 2 per cent in 1919 to about 6 per cent in 1937. Estimates of the Metropolitan Life Insurance Company indicate that the mortality from cardiovascular-renal disease in the United States will increase from 600,000 in 1940 to 1,200,000 in 1960. Perhaps this is a result of our modern life.

During the past few years there has been much progress in the production of hypertension experimentally and in understanding of the mechanism by means of which the blood pressure is elevated in such experiments. A prominent example is the notable achievement of Goldblatt, who produced elevation of the blood pressure in animals by diminishing the blood supply to the kidneys. For these experiments, in which he produced a condition in animals closely resembling essential hypertension of man, Goldblatt received the Phillips Memorial Prize at the meeting of the American College of Physicians two years ago. I do not wish to detract from the excellent work that has been done on experimental hypertension and allied studies, rather, I wish to commend such work as being praiseworthy evidence that advances are occurring in a field of medicine in which little progress has been made until recently. I feel, however, that I shall not detract from this excellent experimental work if I indicate that it has helped only slightly the clinician who must attend patients who have hypertension. Up to the present time the only clinical benefit has been the knowledge that occasional removal of a diseased kidney may cause blood pressure to return to normal and limited evidence that renal extracts may reduce blood pressure.¹¹

MEDICAL TREATMENT

Since hypertension is produced by increased resistance offered to the flow of blood through the arterioles the specific need in medical

treatment is a preparation which will restore arteriolar resistance to normal and which will not produce harmful or unpleasant side effects. Unfortunately, such a preparation is not available now.

It is well to state herein that the belief, which persists stubbornly, that it is inadvisable to lower blood pressure in the presence of essential hypertension has no foundation in fact. In my experience with uncomplicated hypertension vital functions continue normally when blood pressure is reduced and I doubt that reduction of blood pressure in itself is harmful. I believe that such a reduction is highly desirable in uncomplicated hypertension.

It has been shown repeatedly that blood pressure is not static but is labile. This is particularly true in the presence of hypertension, when the blood pressure fluctuates greatly. Hines and I¹² have shown that if the systolic blood pressures of a group of patients in the clinic were more than 200 mm of mercury, subsequent readings in the hospital would show that the systolic blood pressure decreased an average of about 50 mm of mercury and that the average for the diastolic blood pressure decreased about 35 mm of mercury, when no specific treatment was administered.

If all physicians who wrote of reduction of blood pressure as resulting from some specific method of treatment would determine the blood pressure of their patients hourly for twenty-four consecutive hours, they would not err in attributing to the treatment those reductions in blood pressure which occur without specific cause. There can be but little doubt that the popularity of many remedies is based on observation of diminution of blood pressure, a diminution which has occurred spontaneously and has not resulted from a specific remedy. Recently Kapernick,¹³ working with me, has studied extensively the effects of a number of compounds on blood pressure. The blood pressure was determined at least twice daily on several groups of patients confined to a state hospital. After a control period of a week during which no medicine was given, various remedies were tried. The conclusion was that padutin, phenobarbital, hepvisc, iocapral, allimin, erythrol tetranitrate, aminophylline, theominal and theobromine do not reduce blood pressure significantly. Similar studies carried out in England¹⁴ have shown similar results. A large number of remedies were found to be less valuable in reducing blood pressure than placebos were. There is much hope that renal extracts will prove to have clinical

value but at the present time results are uncertain although very encouraging ¹¹ Renal extracts are not as yet available for clinical use

Potassium sulfocyanate has been used in the treatment of hypertension for several years ^{15, 16} A relatively recent and important advance has been determination of the concentration of the cyanates in the blood by Barker ¹⁷ The amount of this drug to be administered orally should be determined by frequent calculations of the concentration of cyanates in the blood ¹⁸ The concentration in the serum should range between 8 and 14 mg in each 100 cc of blood As little as a total of 5 grains (0.3 gm) a week, or as much as 5 grains (0.3 gm) three times daily, of potassium sulfocyanate, depending of course on the individual patient, must be administered to cause the aforementioned concentration in the blood I give my patients 6 grains (0.4 gm) daily to begin with and determine concentration of cyanates in the blood in one week Subsequent dosage and the frequency of determination of concentration in the blood depend on individual responses When the dosage is stabilized, determination of the blood cyanates every three to four weeks is adequate Many physicians who cannot use large laboratories object to the use of cyanates because they have trouble obtaining an analysis of blood Actually the technique is no harder than is the determination of urea in the blood and any technician can learn it A kit* for office determination of cyanate in the blood is available While the method includes matching colors, it has been in my experience fairly satisfactory except that the values found are likely to be higher than values determined chemically

Such symptoms as headache, insomnia and nervousness may be relieved by treatment with cyanates Fatigue, weakness, increasing nervousness, dermatitis, nausea, vomiting, anemia and enlargement of the thyroid gland may occur, even if administration of the drug is well controlled ¹⁹ Weakness and fatigue may occur early in the course of adequate treatment, but usually they disappear as medication is continued After five to ten years of treatment, elderly patients who have severe grades of hypertension may have anemia, emaciation and muscular wasting but it is not clear whether these conditions result from cyanate therapy or from hypertension itself If the concentration of cyanates in the blood is too great, lethargy, mental confusion, psychosis, exfoliative dermatitis, weakness, difficulty of speech, convulsions and

* Made by Eli Lilly and Company

collapse may occur. In my experience and that of my colleagues with the use of sulfocyanate there is definite reduction of blood pressure in more than half the cases. Certainly it is the most satisfactory drug available today for treating hypertension. Potassium sulfocyanate never should be administered for a long period unless the amount administered is based on studies of concentration of cyanates in the blood of each patient.

Rest and the reduction of nervous stresses and strains are advisable in the treatment of many patients who have essential hypertension. In general, it is advisable for patients who have hypertension to obtain nine hours of rest in bed at night, to lie down for an hour or an hour and a half in the middle of the day, to take vacations frequently, to acquire a calm, philosophic outlook on life and to avoid nervous stresses and strains. Young individuals who follow occupations that are strenuous from a nervous standpoint may well consider it advisable to change to an occupation that is more restful. Houston²⁰ has emphasized that hypertension responds less readily, the closer each individual patient is to the necropsy table, and has stressed the need for treatment in the early phases of hypertension or indeed before hypertension affects those who eventually will probably be afflicted with it. He wrote

"The gravity of the threat offered by essential hypertension will justify an alteration of occupation in an attempt to seek a calmer social environment. The threat justifies our using our wits in every way we can to get a better understanding of what is meant by habit and emotional attitude in the specific case before us. The study of habit as found in John Dewey's 'Human Nature and Conduct', the study of the possibility of gaining control of the involuntary muscular action of the arteriole through a perfected control of the skeletal muscle as outlined by Jacobson in 'Progressive Relaxation' will prove helpful for understanding. It may prove helpful to realize that the 'will to power' as celebrated in success magazines and popular success psychologies constitute propaganda for emotional habits and attitudes which may in some instances be baneful, and that the doctor himself may be a therapeutic agent of great value if he can successfully propagandize and institute a different habit, the habit of equanimity, of 'Power through Repose' (See Anna Payson Call's excellent popular book under this title). While any emotion represents some break of smooth flow of feeling or action, emotional attitude that leads to essential hypertension

seems to be one in which a curb is placed on a strong need for action, a sense of social urgency menaced by frustration. Hard labor doesn't produce hypertension, but stress, strain, striving imply a need of action generated by social requirements but that has met with social obstacles."

Many diets have been advised for the treatment of hypertension, but there is very little evidence that diet influences blood pressure. We do not feel it advisable to restrict protein in diets of hypertensive patients who do not have renal or myocardial failure. F. M. Allen²¹ originally suggested restriction of sodium chloride in essential hypertension. He found reduction of blood pressure to normal in 19 per cent of hypertensive patients who received this treatment and marked reduction of it in 42 per cent. He stressed that the salt-free diet should be secured by selection of foods which had a small content of salt and by failure to add salt in the kitchen or at the table. The salt-free diet is not looked on favorably by most students of hypertension today. I myself cannot speak authoritatively, because my experience with well-conducted studies of the method has been small. Certainly it is useless to tell a patient not to add salt to his food. If a patient is to be treated with salt restriction, he should be treated scientifically as one treats a patient with diabetes. If an adequate period of observation does not show reduction of blood pressure, this method of treatment should be abandoned.

Individuals who are overweight should reduce, for obesity throws an additional strain on the heart by increasing the work that it must do and as a result of deposition of fat in cardiac muscles and around the heart. There is some evidence also that reduction of the weight of obese people reduces blood pressure. Restriction of alcohol and coffee is not imperative unless they serve as stimulants. They do not in themselves increase the blood pressure. Indeed alcohol reduces it temporarily. Smoking greatly increases the blood pressure of many patients who have hypertension, and if this can be demonstrated by having the patient smoke after his blood pressure has reached a basal value, it is well to consider sharp restriction or complete elimination of smoking.

It is apparent that the methods of medical treatment available today are largely unsatisfactory, so far as reduction of blood pressure is concerned. That they have some value is apparent, but I believe that almost every physician who treats hypertension is dissatisfied with such therapeutic methods as are available to him today. Symptoms may be

relieved rather easily, as Ayman has pointed out. However, continued relief of symptoms may be considerably more difficult to accomplish than is temporary relief of them. Headache is the most annoying symptom of the uncomplicated stage of hypertension and there has been no satisfactory method of relieving it. It characteristically occurs in the early morning hours, it either awakens the patient or is present when the patient wakes at the usual time. It usually is described as consisting of sensations ranging from a dull ache to a severe pounding distress and it usually is located in the cervico-occipital region. Ordinarily it disappears after the patient has been active for several hours.

For many years I have been puzzled about the mechanism of hypertension headaches. The designation of them implies that they result from high blood pressure but determinations of the blood pressure of patients with hypertension hourly during rest and sleep indicate that the blood pressure decreases markedly during sleep and then when the headaches occur, the blood pressure, although elevated, is lower than it is during the periods of activity. Therefore, there must be some other explanation for hypertension headaches than the level of the blood pressure. Since the headaches occur at night during rest in the horizontal position, MacLean and I²² felt that they might arise as a result of this horizontal position. Obviously, in order to study this condition thoroughly, patients who were having headaches almost every morning were needed in order to avoid interpreting spontaneous remissions of headaches as the result of therapy. Since our original report we have had less success in relieving hypertensive headache by having patients sleep in the "head-up" bed than we had anticipated, but the method should always be tried, and discarded if found to be without value.

My conclusion relative to failure of reduction of blood pressure by medical means is supported by the opinion of almost all those who treat patients who have high blood pressure under controlled conditions, by the high mortality caused by hypertension, and by the number of physicians who consult other physicians or refer their patients to other physicians because the physician's own medical treatment has been unsuccessful. The situation regarding the medical treatment of hypertension is roughly comparable to that regarding pernicious anemia before the discovery of the efficacy of liver extract. It may surprise younger members of the profession to know that the present-day medical treatment of hypertension is much the same as that outlined

twenty-five years ago by Elliott and that described twenty years ago by Moschcowitz with exception of the use of potassium sulfocyanate. During the intervening period several million people have died of high blood pressure in the United States. The failure to change this type of medical treatment is patently not referable to the fact that this treatment has been satisfactory but to the fact that there has been nothing better brought forth.

These observations do not release physicians from the responsibility of treating patients with hypertension. They must care for many patients with conditions for which there are no specific remedies, as for example, leukemia, chronic nephritis, lymphosarcoma, carcinoma and degenerative diseases of the nervous system. If the physician allays the patient's fears, does not subject him to inconveniencing therapeutic procedures which have no benefit, and keeps him from the hands of irregular practitioners who treat him for his monetary value, then the physician has done the patient a service. Intelligent supervision and judicious use of sedatives are helpful. If in addition the patient's blood pressure can be reduced by the use of other measures which I have discussed, the physician has added to his service to the patient.

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PNEUMOCOCCAL AND "VIRUS" PNEUMONIA*

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SO MANY excellent papers have recently been published describing clinical experiences with sulfonamide chemotherapy in pneumococcal pneumonia that it is quite needless, in the absence of any new facts, to discuss the matter at length here. Without exception, there is agreement among all observers as to the epochal nature of the discovery of chemicals which have an almost specific value in the treatment of pneumococcal infection, particularly pneumonia. There are, however, still many questions which have not yet been fully answered, five of which may be posed as follows:

1. *Is the introduction of sulfonamide therapy alone sufficient to explain the striking diminution in the death rate from pneumonia in the last few years?*

At present it is possible only to estimate the actual value of chemotherapy in pneumonia. Because of the justifiable enthusiasm attendant upon its use, there is, I believe, an understandable tendency to exaggerate the extent of the gains achieved with chemotherapy and to ignore some other factors which may also play a role. Let me cite an example to illustrate the point.

Without critical thought, a glance at a recently published chart¹ of mortality from pneumonia which shows a strikingly low death rate from pneumonia in 1938-39 as compared with 1928-29, might be taken to indicate a triumph of chemotherapy. If, however, similarly gathered statistics of other recent years are examined, the "pneumonia death rate was at a record low" in 1937-38.² Beginning in August 1937, every month except two showed a lower mortality rate from pneumonia than did the same month in any other year since 1920. According to another statistical report³ by the U. S. Bureau of Census the mortality rate from "influenza and pneumonia" dropped from 207 per 100,000

¹ Presented October 17, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

in 1900 to 114 per 100,000 in 1937. The period covered by these statistics, of course, was before chemotherapy for pneumonia was available. The increasing use of serotherapy may have played a role, but hardly enough to account for so great a reduction in mortality. Before discovering what were the important factors in lowering the death rate, it would first be necessary to know the morbidity rate of the disease. If the morbidity rate is stationary and the mortality rate reduced as much as stated there would then be reason to acclaim the success of specific therapy. Accurate figures, however, are not available. A significant fact is that in one study a drop of 27 per cent in mortality occurred in the first quarter of 1940 as compared with a like period in 1939.⁴

It is probable that numerous factors are at play. In the control of typhoid fever, for example, increased knowledge of the disease, specific vaccine, improved sanitation, improved diet, control of carriers and other measures all combined to reduce its incidence. Similar factors were operative in tuberculosis. The lowest death rates in history were also recently recorded for diarrheal diseases, appendicitis, and puerperal conditions. Whether or not serotherapy and chemotherapy are alone responsible for the recent low death rate in pneumonia, or whether its prevalence like that of other diseases is cyclical, and the present low ebb is merely a phase, only the future can tell.

Indications are also suggestive that other unknown factors may be operative. For example, in our own experience in 1939⁵ with an infection of the respiratory tract, probably caused by a filtrable agent, pneumococci were surprisingly scarce. They were isolated from the sputum of only 8 out of 100 patients. It is generally believed that from 35 to 50 per cent of normal persons carry pneumococci in their nasopharynx habitually, and mild infections of the respiratory tract supposedly increase the percentage still more. The paucity of pneumococci in our own recent experience may indicate a temporary diminution in their numbers and prevalence in certain localities as a result of conditions totally unknown.

2 *Should chemotherapy be started as soon as evidence of pulmonary infection is detected?*

In this matter also, I believe enthusiasm has somewhat exceeded sound practice. On several occasions I have read printed advice recommending that chemotherapy be started as soon as a diagnosis of pneumonia is made. It would be far better, and in accord with facts, if the

recommendation were restricted to cases of clinical lobar pneumonia, or better still to cases of pneumonia caused by the pneumococcus or by the hemolytic streptococcus. Chemotherapy may also be effective in staphylococcal pneumonia. There are, on the other hand, many forms of pneumonia in which chemotherapy with the drugs available at present is of no value. Obviously every patient with fever and a few rales in the lung should not be subjected to the discomforts and hazards of chemotherapy. The sulfonamide compounds have not yet been shown to have any influence on influenza or other influenza-like pulmonary infections which have been prevalent in recent years, nor are they of value in pulmonary congestion, or in mixed infection of the lungs where bacteria susceptible to the sulfonamide compounds are not present. The important point to be made is that etiologic diagnosis should govern the type of therapy to be employed.

In recent experience I have seen a number of patients with sulfanilamide poisoning to whom the drug was given without previous attempt having been made to discover the cause of the pneumonia which was atypical in each case. In such cases, in the absence of beneficial effect after a reasonable trial of the drug, instead of stopping it, more and more is given until poisoning results. It is just as important to know when not to use chemotherapy, and when to stop it, as it is to know when to use it. It would be important to know how many patients who supposedly die from an infection, actually die from drug poisoning.

The matter of giving sulfonamide compounds to prevent the development of pneumonia has been raised. There is at present no basis for their use as prophylactics. If, for example, only 1 person out of a 1000 who has a cold develops pneumonia it is hardly justifiable to treat the other 999 with the drugs. The one person who may develop pneumonia can be treated promptly and properly after pneumonia occurs, provided it is caused by bacteria amenable to therapy. Perhaps the same reasoning may apply to the question regarding the use of sulfonamides to prevent postoperative pneumonia.

Our practice during the past winter has been as follows. When an adult patient had pneumonia which commenced in the "typical" manner, that is, suddenly with a chill, a pain in the chest, cough, rusty sputum, high fever and leukocytosis, 4 gm of sulfathiazole was promptly given by mouth. During the next few hours, before the next dose of 1 gm was due, the sputum was examined and the type of

pneumococcus, if present, determined. The dosage was then continued at 4 hour intervals until the temperature fell to normal and clinical recovery was evident. We have as yet had no recurrences after stopping the drug at this time.

If, however, a patient with pneumonia became ill gradually, more or less as an aggravation of a cold or influenza, without the typical symptoms and signs just mentioned, and if the leukocytes were normal or reduced in number, no sulfonamide compounds were given, unless in the examination of the sputum pneumococci of types I, II, III, V, VII, VIII or XIV or hemolytic streptococci were present in numbers sufficient to regard them as etiologically significant. Blood cultures were of course, made routinely in all cases.

3 *When and how should serum therapy be employed?* There is much evidence available that chemotherapy is just as effective, if not somewhat more so, than specific immune serum in the treatment of pneumococcal pneumonia. This being the case, it would seem that serum is necessary only in the exceptional case. On the other hand, experimental studies show conclusively that the combination of chemotherapy and serotherapy has greater therapeutic value than either method used alone, but not enough time has elapsed to serve final judgment in the matter as regards its clinical value. Both serum therapy and chemotherapy used separately are said to reduce the mortality rate to between 3 and 10 per cent in different series of cases, and in several of them chemotherapy seems to be superior in effectiveness. Here again caution is needed in interpreting statistics. It is highly probable that while the complexity and expense of giving serum generally precludes its use for all but seriously ill patients, chemotherapy with its ease of administration and cheapness, is used much more freely and given to patients who are not seriously ill and who perhaps wouldn't be, even if untreated. Hence the recorded mortality with chemotherapy may be lower. Chemotherapy should be used alone in patients who are known to be hypersensitive to both horse and rabbit serum, when for some reason the causative pneumococcus cannot be typed or when serum cannot be obtained. Serotherapy should be employed alone in patients who are known to be sensitive to, or poisoned by, sulfonamide compounds. Combined serum and chemotherapy seems to be indicated in about 10 per cent of cases of pneumococcal lobar pneumonia.

There are a few criteria to govern whether specific antipneumococ-

cus serum should be given together with sulfathiazole. They are as follows

- a If chemotherapy has been given for 18 to 24 hours without causing improvement
- b In patients over 40
- c In pregnant women or in early puerperium
- d When more than one lobe is involved and when the blood culture is known to be positive

4 *How do the sulfonamide compounds exert their beneficial effect in pneumococcal infections?*

At present it seems that the presence of sulfonamide compounds in some way interferes with the nutrition of bacteria so that they die off for want of food. If Lockwood's interpretation of the mechanism is correct, much depends upon the amount of nutritive peptone or other substances which is required for bacterial growth. If an abundance of nutritive material is present it may be great enough to overcome the effect of the sulfonamides and permit bacteria to thrive in spite of chemotherapy. This may be the reason why chemotherapy is of no avail in localized purulent pneumococcal disease such as arthritis or empyema, yet on this basis it is difficult to explain the striking effects of chemotherapy in some cases of pneumococcal meningitis in which pus is also present.

It is obviously a matter of great importance to discover just how the sulfonamide compounds affect pneumococci. Once this is known, it may pave the way for the development of better agents, ones which harm the bacteria more and the patient less.

5 *What is the likelihood of the future discovery or synthesis of other similar or dissimilar chemicals to cure pneumonia?*

From the rate of progress in the past few years in the chemistry of sulfonamide compounds and from the number of scientists studying the problem, there is every reason to hope for the development of even better chemicals with which to combat pneumonia. Of great interest were the studies of Avery and Dubos concerning the lytic effect of a certain enzyme on the capsular substance of type III pneumococcus. Although this enzyme is capable of curing experimentally induced pneumococcal infections in animals its use in man has not as yet been thoroughly studied. Recently an even more interesting enzyme called Gramicidin has been prepared by Dubos which serves to destroy all

gram positive bacteria Success in using this new enzyme has already been attained in treating mastitis of hemolytic streptococcal origin in cows Reports of the effect of this substance on pneumococcal infections are anxiously awaited

"VIRUS" PNEUMONIA

During the past three years, especially in the winter months, an atypical form of pneumonia which could not be diagnosed on an etiologic basis was observed in Philadelphia and elsewhere Because of its resemblance to cases of genuine influenza virus pneumonia and to the pneumonia which occurs in psittacosis and vaccinia, and because an elusive virus was isolated from a few patients, it was suggested that the term "virus pneumonia" be applied to the disease if it could be proved that a virus was the cause Proof has thus far not been offered, hence the use of the term at present is not fully justified Moreover, in subsequent studies I have shown that the term pneumonia only includes a few severe cases among a large number of less severe cases of the same disease in which the lungs are not involved Therefore pending the discovery of the causative agent, I have called the disease "grip" or "an epidemic infection of the respiratory tract" It is probable that it is one of several stable or variable specific entities similar to, or related to epidemic influenza which Francis has just discussed It is also probable that it is not a "new" disease, but a newly recognized disease which has been prevalent as long as influenza, and is separable from it only by special, recently developed methods of identification

The disease has been described in several published papers^{5,6} In the epidemic studied at Jefferson Hospital in 1939 about 50 per cent of the nursing staff and student body were ill Of these, 75 per cent were ambulatory and complained chiefly of coryza, nasal obstruction, frontal headache, weakness, dizziness, sweating, and anorexia lasting for several days Relapses were common

About 25 per cent had to go to bed with similar but severer symptoms All of these patients had tracheobronchitis Actual pneumonia was detected in only 6 per cent of the whole group

In patients with pneumonia, the onset was gradual with the symptoms and signs of the mild form of the disease, but instead of improving they became worse Photophobia and a dry, unproductive, persistent cough developed Profuse sweating and occasionally dyspnea and

cyanosis occurred. In most cases the lining of most of the respiratory tract seemed to be involved so that a descriptive but cumbersome name for the disease in its severest form may be nasopharyngotracheobronchopneumonia. Signs of atypical pneumonia in one or both lungs gradually appeared, and in some cases pneumonia was first discovered by roentgenography.⁷ Typical signs of consolidation were seldom present.

Sputum was seldom raised and in that obtained, the usual "mouth" flora of bacteria were present. Pneumococci, surprisingly, were found in only 8 of 100 samples of sputum tested and they were of the higher numbered types. They probably had no etiological significance. The leukocytes were usually normal in number but tended to increase slightly as the disease progressed.

All patients recovered, so that no necropsy material was available for study to determine whether or not the pulmonary reaction resembled the form usually elicited by pathogenic filtrable viruses.

The treatment was symptomatic and in a few patients sulfanilamide was given experimentally with no apparent effect on the course of the disease.

ADDENDUM

Since this paper was prepared, a number of other pertinent studies of similar or identical respiratory tract infection have been published. In two of them^{8, 9} necropsy showed an unusual form of pneumonia characterized by a bacteria-free mononuclear cell infiltrate. In four other studies,^{10, 11, 12, 13} published almost simultaneously, report is made of the isolation of filtrable agents from patients with infections closely resembling the ones called virus pneumonia. Studies are under way at present to determine if the "virus" pneumonia described here is etiotologically related to any of these newly reported ones.

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NEWER KNOWLEDGE OF THE VITAMIN
B-COMPLEX*

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OUR newer knowledge of nutrition has resulted mainly from clinical studies made possible by the isolation and synthesis of many of the vitamins by the biochemists. In 1920 none of the vitamins then known, vitamins A, B₁, B₂, C and D, had been chemically identified or synthesized. By 1940, all of the vitamins distinguished alphabetically in 1920 have been identified chemically and synthesized. In addition, vitamins E, K, P, and ten or more additional B-vitamins have been discovered. Of these, alfatocopherol, several naphthoquinones, nicotinic acid, pyridoxin, and pantothenic acid have been synthesized. These discoveries of the biochemists, if applied to the prevention and treatment of human disease, may be compared, in importance, to the discoveries in bacteriology made in the decades on either side of 1900.

Application by clinical investigators of the biochemical discoveries made in the group of B-vitamins has been so rapid that in this review the title "Newer Knowledge" will be arbitrarily defined as including only 1939 and 1940.

The vitamin B-complex is now known to contain at least a dozen fractions, five of which are available in crystalline form in amounts adequate for clinical use. These are thiamin hydrochloride (B₁), riboflavin (B₂), nicotinic acid (p-p factor), pyridoxin (B₆) and pantothenic acid (filtrate factor). Through the controlled use of these crystalline B-vitamins, clinical investigators have made, in the past two years, progress far beyond what was possible when only concentrates were available. This progress may be summarized broadly as follows:

1. Additions to our knowledge of the clinical manifestations of a deficiency in the B-vitamins

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- 2 Additions to the list of diseases known to be due to nutritional deficiency
- 3 The increasing recognition that deficiency disease in man is usually not single but multiple
- 4 The development of laboratory methods to aid in the diagnosis of deficiency diseases
- 5 The recognition of the necessity for restoration to staple foods of vitamins removed in processing

THIAMIN HYDROCHLORIDE

Our newer knowledge of thiamin hydrochloride consists in additions to the list of its deficiency manifestations, and in the development of laboratory methods for its quantitative determination in blood and urine. As application of these methods to the diagnosis of thiamin deficiency is still in the early experimental stage, they will not be treated in detail.

In February 1939, before this audience, I¹ divided the clinical manifestations into (1) anorexia and fatigue, (2) a neurologic syndrome, and (3) a circulatory syndrome. At the present time the neurasthenic syndrome replaces anorexia and fatigue, and part of Wernicke's syndrome is added to the neurologic manifestations. No significant additions have been made to our knowledge of the circulatory syndrome.

The neurasthenic syndrome is probably the most common manifestation of isolated vitamin B₁ deficiency. As in neurasthenic syndromes of any origin, the symptomatology is varied but its outstanding characteristics are anorexia, fatigue and insomnia. Completing the picture of neurasthenia are such complaints as irritability, "gas," nausea, constipation, uncomfortable sensations in the abdomen and other parts of the body, depression, backache, headache (usually of the occipital or constricting band type), sighing, palpitation, and precordial distress. For several years I have been cognizant of this group of symptoms in patients having the objective signs of vitamin B₁ deficiency. I usually attributed this group of symptoms to neurasthenia on the basis of an abnormal psyche which led to further dietary restrictions and, in turn, to the development of objective signs. I still believe this to be true of certain patients. Adequate treatment for the deficiency was followed not only by disappearance of the objective signs but also, again in certain instances, of the neurasthenic syndrome. I then applied, to sub-

jects having the neurasthenic syndrome without objective signs of vitamin deficiency, the treatment-regimen of dietary correction, vitamin supplements rich in the entire B-complex, and thiamin hydrochloride. Many of these patients, though not all, were helped. The improvement was attributed to better nutrition plus the psychotherapy of this dietary regimen. Not until Williams, Mason, Wilder and Smith,² in a well-controlled experiment with human subjects, reproduced this characteristic neurasthenic syndrome by inducing an isolated thiamin deficiency, have I been willing to include it as a manifestation of vitamin B₁ deficiency. It should not be inferred, however, that all neurasthenia is based on thiamin deficiency. Such is definitely not the case. Almost any agent causing the triad of anorexia, fatigue, and insomnia, if not soon relieved, will cause, in susceptible persons, the development of other neurasthenic symptoms. Nevertheless, the proportion of neurasthenia caused by vitamin deficiency may be larger than is now commonly believed.

Williams, Mason, Wilder and Smith, in their subjects in whom isolated thiamin deficiency was experimentally produced, noted the regular development of electrocardiographic abnormalities. "They consisted of diminution in the amplitude of all complexes and particularly of the T waves of the chest leads. In certain instances the T waves became isoelectric or shallowly inverted. On restitution of thiamin to the diet the electrocardiograms became normal." These observations of the Mayo group confirm the findings of Jolliffe, Goodhart, Gennis and Cline,³ in whose experimental subjects precordial pain and electrocardiographic abnormalities were likewise observed. It may be that in persons past middle age the coronary arteries have at times been unjustly condemned on the history of precordial pain plus abnormalities in the electrocardiogram.

The central neurologic manifestations of thiamin deficiency occur only after peripheral polyneuropathy is evident, and form a part of Wernicke's syndrome. As demonstrated by Jolliffe, Wortis and Fein,⁴ the oculomotor palsies of this syndrome are a vitamin B₁ deficiency manifestation and respond to adequate dosage of thiamin hydrochloride. On occasion the stupor will respond to similar therapy, but the ataxia shows no such response. The syndrome as originally described by Wernicke is a multiple deficiency, and the clinical picture seen is dependent upon the multiplicity of factors involved.

RIBOFLAVIN

Our clinical knowledge of riboflavin deficiency dates back only to December 1938 when the preliminary note of Sebrell and Butler⁵ appeared

The lesions produced by Sebrell and Butler in women maintained with the diet of Goldberger and Tanner appeared 94 to 130 days after the beginning of the experiment. They began "as a pallor of the mucosa of the lip in the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, and within a few days superficial transverse fissures appeared, usually bilateral, and exactly in the angle of the mouth. In some instances the fissures continued onto the skin for a distance of as much as half an inch. These lesions resemble those described as *perlèche*. At about the time the fissures were seen, the lips became abnormally red along the line of closure. This was due, apparently, to a superficial denudation of the mucosa. In addition to the cheilosis, there was also seen a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the *alae nasi*, in the vestibule of the nose and on the ears." Kruse, Sydenstricker, Sebrell and Cleckley⁶ have reported, in addition, a keratitis associated with these signs of riboflavin deficiency.

Jolliffe, Fein and Rosenblum⁷ have reported fifteen subjects having lesions due, we believe, to riboflavin deficiency. Thirteen of these subjects were alcoholic, one had advanced pulmonary and intestinal tuberculosis, and one was an epileptic. In this group of fifteen patients thirteen also had nicotinic acid deficiency, seven, vitamin B₁ deficiency, and three, vitamin C deficiency, while only one showed no clinical evidence of another vitamin deficiency. Since then, however, we have observed many subjects having a cheilosis which responded to treatment with synthetic riboflavin, who presented no clinical evidence of another deficiency disease. The facial lesions seen in the fifteen cases reported consisted of *filiform* excrescences of a seborrheic nature, apparently derived from the sebaceous glands, varying in length up to 1 mm, closely to sparsely scattered over the skin of the face. Their characteristic location was in the nasolabial folds, but in addition they occurred frequently on the *alae nasi*, occasionally on the bridge of the nose, and sometimes on the forehead above the eyebrows. The skin on which the excrescences were located was the seat of a fine, scaly, greasy desquamation. On

casual inspection these filiform lesions resembled urea frost, but they could not be brushed off by rubbing with the fingers. In addition, most of the patients showed fissures and maceration at the angles of the mouth, and a degenerative crustlike formation on the epithelium of the lips, most marked on the lower. The fissures at the angles of the mouth were bilateral and extended laterally 1 to 3 mm onto the mucous membrane of the mouth and 1 to 10 mm onto the skin. They were usually very shallow but sometimes were 0.5 mm deep, and their bases as a rule showed little or no increased redness. Extending for 5 to 20 mm from the angle of the mouth onto both lips, the mucous membrane was macerated and wrinkled and pearl-gray. The lips, particularly the lower, frequently showed a marked increase in the vertical fissuring, often without a break in the mucous membrane. Occasionally the vestibule of the nose was involved with lesions similar to those on the lips.

By maintaining patients having these characteristic lesions of riboflavin deficiency with a control diet poor in the B-complex, we demonstrated that these lesions respond to the administration of synthetic riboflavin, but not to thiamin hydrochloride, or nicotinic acid.

NICOTINIC ACID

The signs and symptoms of partial chronic nicotinic acid deficiency, particularly those occurring in pellagrins, are so well known that it is not necessary to describe them in detail. The complete picture consisting of a scarlet-red stomatitis and glossitis, diarrhea, bilateral symmetrical dermatitis, and mental aberrations, forms in combination such a characteristic syndrome that it is widely known and should never go unrecognized. It is not so well understood, however, that the oral lesions, the gastrointestinal lesions, the mental changes or the skin lesions may each occur alone or in any possible combination. For example, patients having the stomatitis of nicotinic acid deficiency are too frequently considered to have only the superimposed Vincent's infection. The primary diagnosis is not considered and specific therapy is neglected. If nicotinic acid therapy is instituted, not only is the scarlet-red stomatitis blanched within 24 to 48 hours, but the Vincent's infection heals without other general or local therapy. Then mental changes may precede the skin, gastrointestinal or oral changes, and the patients may be labeled as neurasthenic, neurotic or psychoneurotic. Similarly, gastrointestinal manifestations may precede all the others, and the diagnosis

may be missed for many weeks

Jolliffe, Bowman, Rosenblum and Fein⁸ have reported 150 cases of an "encephalopathic syndrome," a condition heretofore almost always fatal, which is caused, it is believed, by nicotinic acid deficiency. This syndrome may occur as the only clinical manifestation of a deficiency disease or it may occur in association with pellagra, polyneuropathy due to vitamin B₁ deficiency, the oculomotor disturbances of Wernicke's syndrome or scurvy. The clinical picture of this encephalopathic syndrome is more or less well-defined and is characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. The vigorous use of nicotinic acid has reduced the mortality in this syndrome from almost 100 per cent to about 15 per cent.

PYRIDOXIN

A syndrome in man attributable to a deficiency of vitamin B₆ or pyridoxin has not as yet been reported as a distinct clinical entity. In rats, a deficiency of this vitamin is known to cause "rat acrodynia," foci of degeneration in striated and cardiac muscle, and changes in the nervous system, particularly of the columns of the spinal cord. Antopol and Schotland⁹ have recently suggested that vitamin B₆ through its pyridine structure may be involved in the enzyme system concerned in muscle metabolism. In this connection it is interesting to note that Spies, Bean and Ashe¹⁰ have described a syndrome characterized by "extreme nervousness, insomnia, irritability, abdominal pain and difficulty in walking," which disappeared dramatically following the intravenous administration of pyridoxin, but which could not be relieved with nicotinic acid, thiamin hydrochloride or riboflavin. This syndrome, however, has not as yet been observed by others. Antopol and Schotland⁹ have reported the beneficial effect of pyridoxin on muscle strength in six patients having pseudohypertrophic muscular dystrophy, but warned that "it is not to be implied that this group of muscular dystrophies are due to avitaminosis B₆." In addition, we have accumulated evidence that vitamin B₆ plays some part in the adolescent acne syndrome.

Syndromes collectively labeled paralysis agitans, while not directly fatal, usually follow a progressive course, the victims eventually becoming helpless and seeking hospitalization. Since muscular rigidity and

weakness is characteristic of paralysis agitans, and since vitamin B₆ is involved in muscle metabolism, it seemed worth while to test its effect in this syndrome. I therefore selected fifteen patients having paralysis agitans, all of whom were bedfast or chairfast, ten for more than three years, and administered to each 50 or 100 mg of vitamin B₆ hydrochloride by intravenous injection, either daily or every other day. Of the fifteen patients, four showed subjective and definite objective improvement. Two additional patients were subjectively improved. These results were reported on April 24, 1940 before the Minnesota State Medical Association.¹¹ Similar results were later reported by Spies, Hightower and Hubbard.¹² Since then I have treated forty ambulant patients having the paralysis agitans syndrome with pyridoxin. Approximately 20 per cent showed definite objective improvement of dramatic proportions. Improvement in some degree was noted, however, in about two-thirds of the patients. It appears, therefore, that the syndrome of paralysis agitans includes a group of persons whose symptoms, particularly the rigidities and weakness, respond to pyridoxin.

RESTORATION TO FLOUR OF VITAMINS AND MINERALS REMOVED IN PROCESSING

It is not surprising that coincidentally with our newer knowledge of nutrition, the necessity for restoring to staple foods the vitamins and minerals removed in processing should receive increasing attention. "England," to quote from a recent editorial in the *Journal of the American Medical Association*,¹³ "locked in the struggle of total war and conscious of the importance of maintaining at high levels the strength and courage of its people, has fortified margarine with vitamin A and restored calcium and thiamin hydrochloride (vitamin B₁) to flour." In our country, surveys made by Stiebeling and Phipard¹⁴ show the diets of wage earners and clerical workers to contain inadequate or borderline amounts of several vitamins and minerals. The more serious inadequacies were in the B-vitamins, in iron and in calcium. Sebrell¹⁵ has pointed out "that in all probability the nutritional diseases constitute our greatest medical and public health problem, not from the point of view of deaths, but from disability and economic loss." Even the best fed members of our population today consume less vitamin B₁ than did the parish poor of 100 years ago.¹⁶ How has this situation come about here in America?

At the present time the American dietary contains about 650 calories derived from white flour (daily per capita consumption equals 65 ounces), practically vitamin- and iron-free, and an equal number of vitamin-free calories from sugar (daily per capita consumption equals 55 ounces). In combination, these sources account for 50 per cent of our daily average consumption of 2500 calories. They provide about 50 I U of vitamin B₁. In 1840 this same number of calories, derived chiefly from stone ground flour, with sugar accounting for but 25 calories per day, provided a minimum of 600 I U of vitamin B₁, and about a proportional increase in the other B-vitamins. Since 1840 the progressively diminishing consumption of wheat flour, combined with the removal of most of the vitamin and mineral content of the wheat berry by high milling and with the marked increase in sugar consumption has produced reduction by two-thirds of the vitamin B consumption of the American people, bringing it down to levels definitely dangerous from a public health standpoint.

Following the principle that flour should be restored to the vitamin and mineral levels of the flour of 85 per cent extraction, in use a century ago, each pound would have to contain about 166 mg of thiamin hydrochloride, 12 mg of riboflavin, 10 mg of nicotinic acid, 20 mg of iron, and 175 mg of calcium.

Another principle to follow in restoration of flour is to restore in the average amount consumed daily (65 ounces) approximately one-fourth of the satisfactory daily requirement of any vitamin or mineral for which flour is a good carrier. To restore flour to this level, each pound would have to contain about 166 mg of thiamin hydrochloride, 122 mg of riboflavin, 615 mg of nicotinic acid, 100 USP units of vitamin D, 615 mg of iron, and 500 mg of calcium. It is perhaps equally important to set maximum limits on the quantities of these vitamins and minerals added to flour, for there may be certain commercial advantages in claiming a higher vitamin or mineral content. In addition, it is probably in the interest of the consumer that flour should carry only its own burden, and not be fortified to provide for the vitamin and mineral deficiencies of sugar. Each industry should carry its own burden. A satisfactory overage would be 50 per cent in the case of thiamin, riboflavin, nicotinic acid and vitamin D. For iron, the maximum should be about 20 mg per pound to allow for the high iron content of whole wheat, for calcium, as high as 20 grams per pound should be permitted.

in order to allow for the calcium additions to certain self-rising flours

Whichever principle is adopted as a basis for restoring flour to a satisfactory nutritional level, it may be accomplished by three possible methods

1 By retaining these substances in the flour This could be accomplished by milling to only 85 per cent extraction Bread from such flour would be dark brown, and unacceptable esthetically, gustfully and intestinally to a great number of people Nutritionally this method seems preferable, but I doubt whether extensive public health education and publicity could make dark bread acceptable to a majority of the American people

2 By restoring to patent flour the required amounts of vitamin and minerals These substances could be added either by the miller or baker Bread from such flour would be white and its baking qualities unchanged The cost would be about 75 cents per barrel of flour, or one-fourth cent per pound-loaf of bread

3 By a combination of methods Patented processes have already been devised for retaining in patent flour certain streams of the mill, rich in some of these vitamins and minerals, which hitherto had been excluded Partial or absolute deficits can then be made up by adding the required substances Bread from these flours has a slightly creamy color and a "wheaty" taste Another combination method would be to substitute high B₁ baker's yeast for ordinary baker's yeast, and make up the deficit in the other nutritional factors by adding the required substances It may be that in future a baker's yeast will be grown that will contain, in addition to unusual amounts of thiamin, the requisite balance of nicotinic acid and riboflavin, leaving only vitamin D and the minerals to be added to the flour

Whatever method is employed, the restoration of these vital food elements to flour would result in improved nutrition for the entire population

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produce serious disability. The problem of properly immobilizing fractures that have to be transported in order to prevent simple fractures from being compounded cannot be overemphasized. If the compound fracture is present, a prompt debridement of the wound and definite, effective immobilization of the fracture until union takes place should prevent or materially lessen the incidence of this type of bone and joint infection. Should infection occur, adequate drainage must be provided, maintaining immobilization. Our experience at St. Luke's Hospital on the orthopedic service with these infected compound fractures and gunshot wounds has been of a salvage nature. In no instance has the original treatment been under our supervision and it therefore seems advisable to omit their consideration.

In osteomyelitis due to extension from an adjacent soft tissue abscess it may be conceded that earlier and more adequate drainage would greatly diminish the chance of extension to nearby bone. Of this type of osteomyelitis we have had none to treat as our colleagues in surgery and otolaryngology treat the infected fingers and middle ears respectively.

Hematogenous acute osteomyelitis or arthritis is a blood stream infection with a portal of entry or primary focus which in many instances cannot be recognized. Cuts, abrasions, infected blisters and furuncles afford such a portal from the skin to the blood stream, while diseased tonsils or pharynx or even typhoid ulcers of the intestinal mucosa represent various portals from the mucous membranes. This disease occurs predominately in the first two decades of life, and boys are more frequently subject than are girls.

Considering this disease as an acute blood stream infection or bacteremia, the localization in any given bone or joint is only an unfortunate event in its course. The fact that such localization often presents the first tangible evidence of the disease and that it affords a point of surgical attack has led to a cart-before-the-horse method of reasoning in the treatment of this at times terrifying clinical picture.

The minute anatomy of the long bones, which has been carefully studied, affords ample reason for the localization of bacterial emboli at certain recognized sites. The nutrient artery breaks up into terminal arterioles in the metaphysis adjacent to the epiphyseal line and here the infected emboli lodge. There is said to be no phagocytic action in the bone marrow. A vascular thrombosis occurs with death of tissue depend-

ing upon the extent of the thrombosis. This death of bone tissue varies from microscopic to massive bone slough or sequestration. Since bone is a rigid tissue, the formation of slough and repair by new bone or involucrum takes many months in contrast to abscess in soft tissue. The suppuration which attends this infected thrombosis spreads through the cortex of the bone, beneath the periosteum to the soft tissues. In the case of the upper femoral metaphysis, which is wholly within the capsule of the hip joint, such a spread of suppuration invariably results in a suppurative arthritis. Similar suppurative infections of bones adjacent to joints may, if undrained, invade the knee, ankle, shoulder or wrist joints, etc. A suppurative arthritis per se with no preexisting bone involvement occurs at times, due most frequently to gonococcus and less frequently to streptococcus and pneumococcus.

Since the bones most frequently involved in this disease are the long bones of the lower extremity, the pelvis and the vertebrae, i e., those involved in weight-bearing, the question arises whether trauma may not play some role in the localization.

When one considers the fact that the vast majority of known primary foci in this disease arise on the skin, it is not surprising that staphylococcus of various types is the predominating bacterial agent responsible for this infection. On this point, there is universal agreement. It has been stated that as high as 90 per cent of these infections occurring between the ages of two and twenty years are due to staphylococcus. Streptococcus is second in frequency, and in patients under two years of age the frequency of streptococcus infection is high. After streptococcus there follow pneumococcus and *Bacillus typhosus* in that order as causative organisms.

The clinical picture that these patients with hematogenous acute osteomyelitis present is primarily one of sepsis. The primary focus may be lost sight of, or forgotten. The patient is seen with chills, fever, at times between 105 and 106 degrees, leukocytosis up to 80,000 and often profound toxemia. If there is localization there will be severe pain at or near the epiphyseal line of a long bone, limited motion and spasm in the adjacent joint, some swelling due to edema and exquisite tenderness. If such a patient is seen within five to eight days of the onset of illness, the roentgenogram will show little or nothing that is of diagnostic help. In certain fulminating cases death may supervene before any localization in bone takes place.

In differential diagnosis, several diseases must be ruled out. Gonococcus arthritis in a fulminating form may be confusing, but there is usually a history of multiple joint pains before the one joint becomes swollen, red, hot and painful. Aspiration of the joint and culture of the purulent fluid will establish the diagnosis. In scurvy the roentgenogram should show subperiosteal hemorrhage.

Acute rheumatic fever presents a hurdle over which, I must confess, I have tripped on one occasion. This embarrassing situation has been summed up by one surgeon who states that, "When acute rheumatic fever presents an abscess, it's osteomyelitis."

If the patient survives the initial onslaught of the disease and shows localization in a bone or joint, the question of treatment arises, and here there is difference of opinion. Divergence of thought among physicians who are intelligently and carefully studying the same subject with a full understanding that each is talking about the same condition may be extremely helpful. However, it is futile to present a jumble of infected compound fractures, hematogenous acute osteomyelitis and protracted cases of bone infection. Conclusions drawn from such diverse conditions can be of little value.

There is honest and reasonable difference of opinion regarding the proper procedure in the treatment of hematogenous acute osteomyelitis. However, the divergence is not as wide as might be expected. The disease in its onset is admittedly a general blood stream infection, and the treatment must be supportive. Dehydration, toxemia and exhaustion must all be combatted in many instances. Blood cultures should be taken at once and repeated at definite intervals. Many observers lay great stress on the bacterial concentration in the blood as a prognostic aid. A negative blood culture may only signify that at that particular moment there were no bacteria in the blood stream or it may mean that the blood stream infection has burned itself out and has been overcome. When there are consistently but few colonies of bacteria per cc of blood, the prognosis is good, while a persisting large number of bacterial colonies per cc means a grave prognosis. Staphylococcus bacteremia is more serious than that due to streptococcus. The incidence of positive blood culture varies considerably as may be seen in a series of three reports comprising 184 cases. In each instance a blood culture was taken. One series reported an incidence of 34 per cent positive blood cultures and another 67 per cent positive cultures. The average

for the entire 184 cases was 56.5 per cent positive. The incidence of positive blood culture is doubtless influenced by the time after onset of the disease that the culture is taken.

During this period of investigation and supportive treatment, the importance of repeated blood transfusions cannot be overemphasized. Up to this point most competent observers are in agreement. When there is definite localization in bone or joint, opinion varies as to the next step. There are those who claim that any surgery is futile and meddlesome, and even jeopardizes the patient's chance of recovery. Some of these surgeons insist on letting nature evacuate an abscess and others will incise and drain when there is frank pus. On the other hand, a larger group of surgeons believe that after properly fortifying the patient, any recognizable localized suppuration of bone or joint should be drained with minimal trauma and little or no insult to bone or soft tissue. The day of early radical surgery on these patients has gone, leaving a great many needless cripples to haunt our clinics and hospitals as reminders of an era of doubtful judgment when scalpel, mallet and chisel ruled the scene. All surgeons now agree that absolute rest and protection of the infected bone or joint must be secured by plaster-of-Paris bandage or brace.

To date the specific treatment of these infections has been largely unsuccessful. Those few which are due to hemolytic streptococcus have been influenced by sulfanilamide and allied drugs, but the vast majority which are due to staphylococcus have not been helped. I can find no agreement that bacteriophage is helpful in those cases nor that vaccines or sera have any influence.

The mortality in these cases occurs chiefly in the first week or ten days after onset in those patients in the first two decades of life. Since the proven presence of bacteria in the blood stream indicates that the general infection predominates, a higher mortality should be expected among those patients who show this evidence of sepsis. When death occurs, it is due to sepsis and to metastatic spread to soft tissues, pericardium, endocardium, meninges. The reported mortality varies almost unbelievably from 1.5 per cent to 26 per cent. This is probably due in part to the fact that authors are not reporting strictly the same condition. Some will adhere rigidly to hematogenous acute osteomyelitis, while others may include haphazardly cases of infected compound fractures, extension osteomyelitis and bone infections that have been seen

years after onset of the disease. In two recently reported series of cases, strictly limited to hematogenous acute osteomyelitis, the mortality was 9 per cent in 33 cases and 17.5 per cent in 218 cases respectively. It is agreed that it is a serious disease with a relatively high mortality.

When these patients are seen early and carefully and skillfully treated, early healing of the local bone condition may ensue in as high as 50 per cent of the cases. Twenty-five to 35 per cent or more will show sequestration, delayed healing and additional foci in bones and joints. Fifteen to 25 per cent of these cases may be fatal.

Those patients who heal early and remain healed and those unfortunates who succumb, no longer remain a surgical problem, but that intermediate group which presents the phenomena of delayed healing, additional foci, growth disturbances, deformities of bones and joints, contribute to that vast army of chronic suppurative bone and joint infection which haunts our hospitals and outpatient departments. One cannot escape the feeling that much of this is due to ill-advised original surgical treatment, where superimposed on vascular and infectious trauma is the insult of improperly placed incisions, too wide removal of uninvolved bone and failure to immobilize the damaged part.

Here the problem of wound healing is paramount, and various methods of sterilization of the sinuses have been advocated. Almost every known chemical has been tried. Maggots have been depicted as chewing up dead bone while it seems quite likely that their urinary secretions are the only factor of value. Such demonstrations of this method of treatment as I have seen have made me feel the urge to reach for a flit gun.

At the present time in most capable hands the most universally approved treatment of this chronic suppurative infection of bone is debridement, removal of obvious sequestra, a pack of vaseline gauze and application of a plaster-of-Paris bandage for immobilization.

The orthopedic service of St. Luke's Hospital has treated during the past 10 years 56 cases of hematogenous acute osteomyelitis, a mere drop in the statistical bucket. From these patients we have learned a great deal and a debt of gratitude is herewith acknowledged. Thirty-four of these 56 patients came to us during the acute stage of their disease, while the remaining 22 consulted us for recurrence of their original disease, for metastatic foci or for the correction of deformities incident to their original lesions.

Age At Onset The disease is definitely and predominately one of

the first two decades of life Eighty-seven per cent of our patients were under 20 years of age at the time of onset of their disease The age incidence is as follows

1 year and under	6	} 87.5 per cent	21-30 years	2
1-2 years	1		31-40 "	1
2-10 "	24		41-50 "	3
11-20 "	18		51-60 "	1
Total		56		

There were 33 males and 23 females among these patients

THE BONES OR JOINTS INVADDED WERE AS FOLLOWS

Weight bearing Bones or Joints		Non weight bearing Bones or Joints	
Femur—Upper metaphysis and hip joint	16	Humerus	5
Lower metaphysis	17	Shoulder joint with no bone involved	2
Tibia — Upper metaphysis	6	Scapula	1
Lower metaphysis	6	Clavicle	1
Entire shaft	2	Radius	1
Pelvis	2	Ulna	1
Spine	3	Elbow joint	1
Sacroiliac joint	3		—
Os calcis	3	Total	12
Fibula	2		
Ankle and tarsal joints 1 each	2		
Phalanx of foot	1		
Rib	1		
Hip joint without bone involvement	4		
Knee joint without bone involvement	2		
	—		
Total	70		

Among these 82 lesions there were only 8 instances in 5 patients in which a joint was primarily invaded without bone involvement These patients except 1 were under 2 years of age, and the causative organism was proved to be streptococcus in each of the 4 patients whose bacteriological study is recorded

Bacteriology In 34 of the 56 patients the bacterium responsible

for the disease is known. Every patient with hematogenous acute osteomyelitis must at some time have had a positive blood culture. In 26 of our patients in the acute stage of the disease a blood culture was taken and found to be positive in 19, an incidence of 73 per cent. Among these positive blood cultures there were 15 due to staphylococcus and 4 due to streptococcus, an incidence of almost 4 to 1 in favor of staphylococcus.

Cultures from the purulent exudate from the wounds revealed staphylococcus 21 times, streptococcus 3 times and a combination of staphylococcus and streptococcus 3 times.

Staphylococcus was the responsible organism in 79 per cent of the cases by blood culture and in 77 per cent by culture of the purulent exudate.

Each of these 2 bacteria has shown a selective action in this small series. Staphylococcus attacks the bones primarily, and we have no proved case of infection by this organism under the age of 2 years. Streptococcus tends primarily to invade the joints without bone involvement. It was the only known organism responsible in 3 out of 4 instances occurring under 2 years of age.

Treatment. Surgery on these patients presents numerous problems which must be confronted carefully and patiently. Thirty-nine, or approximately 70 per cent, of these 56 patients had a single focus of bone or joint infection, while 11 had 2 foci, 4 had 3 foci, 1 had 4 foci and 1 had 5 foci.

Forty-eight patients either in the acute or protracted stage of the disease required incision and drainage, and of these, 9 patients seen in the acute stage healed rapidly and have remained well with one operation only. The other 39 patients treated with drainage have had multiple operations, many performed in other hospitals, an average of approximately 3.5 per patient.

There were 8 patients who came to us with deformities incident to the ravages of the disease who were subjected to reconstructive operations. With but few exceptions all these patients had a prolonged hospital stay.

COMPLICATIONS

Ankylosis of Joints. *Hip joint.* There were 16 instances in which the upper extremity of the femur was invaded with the hip joint sec-

ondarily involved in each, and 4 instances of primary suppurative infection of the hip joint. The end result is known in 19 of these 20 patients and in no instance did the hip joint escape major damage.

Of the 16 patients with primary involvement of the upper femoral metaphysis and secondary suppurative arthritis of the hip, the end result is known in 15. In 11 patients, spontaneous fusion of the joint resulted, 2 were surgically fused and 2 others need surgical fusion. In each instance among those cases in which it was possible to recover bacteria from the blood stream or purulent exudate, staphylococcus was found. There is no instance in this series in which a staphylococcus infection of the hip joint failed to destroy that joint.

Of the 4 patients with primary suppurative arthritis of the hip joint, 3 of these known to be due to streptococcus, 1 patient died and each of the survivors required an operative stabilization of the joint.

Knee joint. The lower femoral metaphysis, invaded 17 times, showed 4 instances in which the knee joint was secondarily involved, resulting twice in bony ankylosis and twice in fibrous ankylosis with marked limitation of motion. Each of these patients had their initial drainage performed elsewhere. It is our belief that this complication should be prevented in most instances by proper drainage.

Ankle and tarsal joints were each invaded once with resulting spontaneous fusion.

Failure of the tibial shaft to regenerate. We have received from other clinics 2 patients who had massive involvement of the entire tibia and had had the tibial shafts resected. One patient regenerated his tibial shaft and the other failed to do so. This complication is said to occur in 19 per cent of cases in which the procedure is done.

Fracture. There were 2 patients who sustained a fracture of the upper femur at or near the epiphyseal line before coming under our care. They had not been adequately protected by brace or plaster-of-Paris during the acute stage of their disease.

Peroneal palsy. One patient whom we saw had a massive scarring of the posterior popliteal region and a complete peroneal nerve palsy. It must be assumed that his peroneal nerve was divided at one of his drainage operations.

Growth disturbance. Nine patients showed shortening of a leg: 3 under 1 inch, 4 between 1 and 2 inches and 2 from 2 to 3 inches.

One patient with a complete recovery of function following a

primary streptococcus arthritis of his knee had an increase in length of the involved leg of about $\frac{1}{4}$ inch

END RESULTS

We fortunately know the end results in 54 of our 56 patients, a follow-up of over 96 per cent. We have classified our patients as *healed*, with or without disability, and *unhealed*, with or without disability. By disability we mean ankylosis of a joint, shortening of an extremity, limp, pain, etc.

Three patients have died, of our 34 seen during the acute stage. Two of these had acute staphylococcus sepsis and one, an infant, had streptococcus infection of the hip. Each died at about 1 week after onset. This gives a mortality of 8.8 per cent among our acute cases of hematogenous osteomyelitis and arthritis.

OF THE 51 KNOWN SURVIVORS, THE END RESULTS ARE AS FOLLOWS

Without disability			With disability		Total Patients
	No. of patients	Per cent	No. of patients	Per cent	
Healed	26	51	12	23.6	38
Unhealed	5	9.9	8	15.4	13
Total Patients	31		20		51

The 13 patients who are rated as unhealed include 3 at present under treatment. It will be seen that though about 75 per cent of the patients are healed, only a little over half of the patients are healed without some disability.

CONCLUSIONS

1. Our experience in hematogenous acute osteomyelitis and arthritis simply offers corroboration on a small scale of many facts that have been previously noted. It is a disease of childhood and adolescence with males more frequently involved than females.

2. The bacteria responsible have been staphylococcus in nearly 80 per cent and streptococcus in most of the remainder. There seems to be a selective action on the part of these two bacteria, staphylococcus in the main affecting the bone primarily, and if a joint is invaded, it is by extension. Streptococcus tends to invade the joints primarily and predominates in infants.

3 The bones and joints of the lower extremity and other weight-bearing bones or joints are much more frequently invaded than those of the upper extremity. Of the long bones, the femur was most frequently invaded in this series.

4 Approximately 30 per cent of these patients had more than one focus of infection. A secondary invasion into the hip joint invariably has followed a focus in the upper femoral metaphysis. The knee joint in this series has been involved in 23.5 per cent of the cases involving the lower femoral metaphysis, and we feel that this may be unnecessary.

Growth disturbance ensued in about 17 per cent of those cases involving the lower extremities.

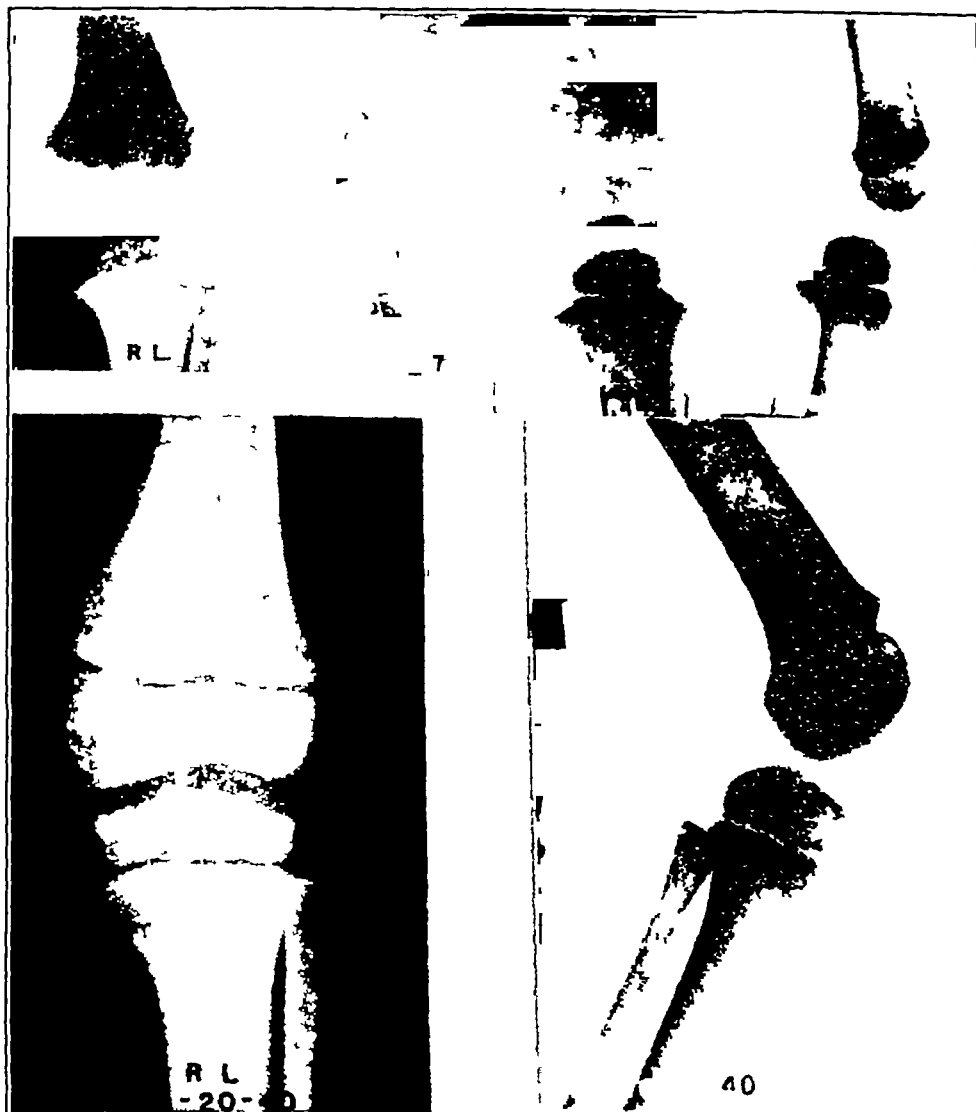
Fractures of diseased bones may be avoided by adequate protection with a plaster-of-Paris circular splint.

5 Approximately 75 per cent of our surviving patients have healed but almost a third of these have disability. Our mortality was 8.8 per cent of the 34 patients seen in the acute stage of their disease.

6 Our treatment of these patients seen in the acute stage of their disease is supportive. Infusions, transfusions, morphine and protection of the involved extremity. When we are satisfied that there is suppuration, rapid drainage through small carefully placed incisions with minimal trauma followed by immobilization with circular plaster-of-Paris splints offers, we feel, the best treatment.

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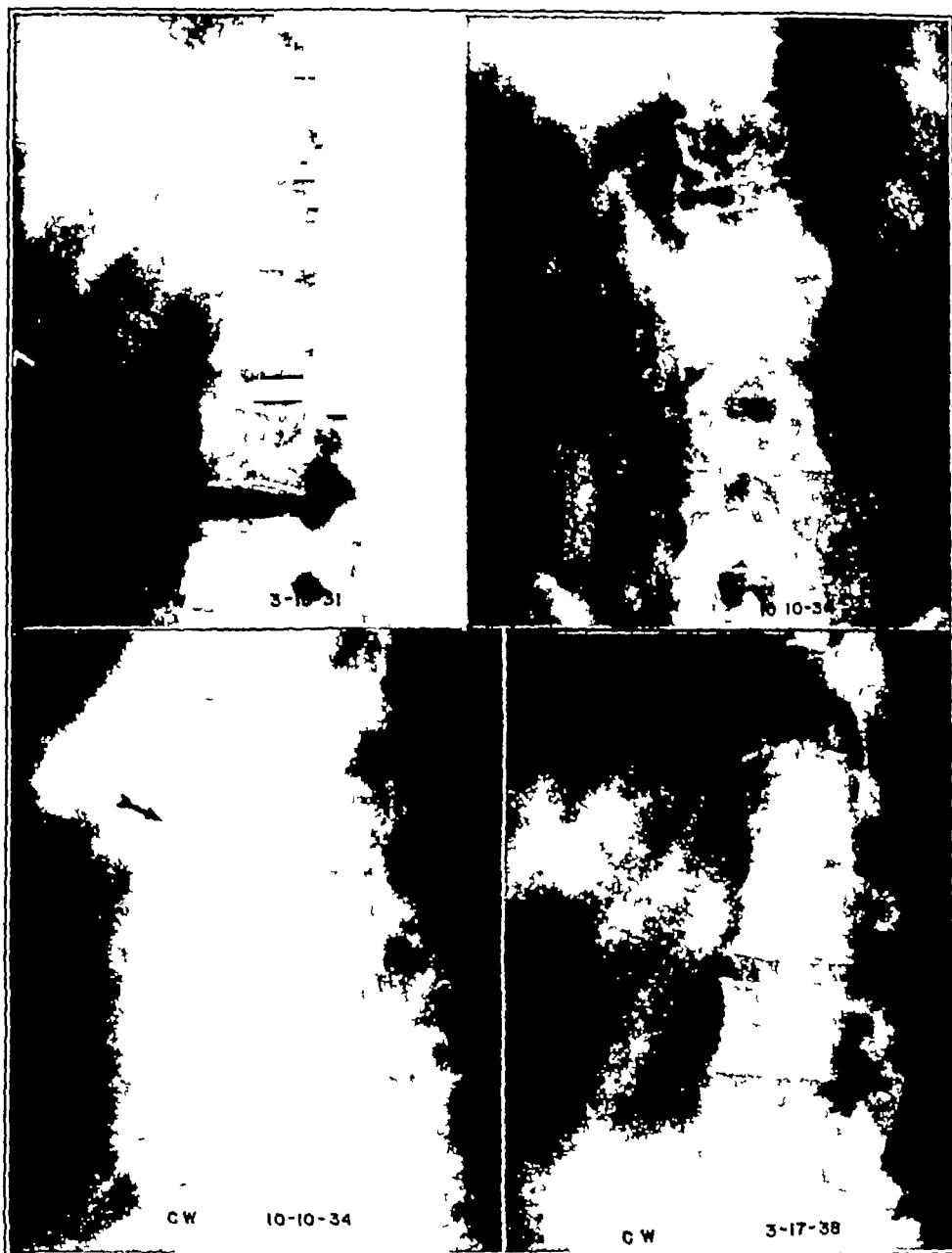
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Case 1—R L, St Luke's No A 10562, male, 19 months of age. He was admitted to St Luke's Hospital March 31, 1937. About one month prior he had a cold and sore throat, and two weeks prior he had swelling of the left knee and fever. His temperature on admission was 104 degrees, white blood cells 80,000. Blood culture was negative. The patient showed effusion into the knee joint and very marked tenderness around the knee. It was not possible to be entirely certain whether this was suppurative arthritis or osteomyelitis involving the lower femoral metaphysis. On incision and drainage, drill holes were placed in the lower femur and upper tibia but no pus was found. However, the knee joint showed 20 cc. of pus which on culture was proved to be hemolytic streptococcus. The knee joint was drained by medial and lateral parapatellar incisions. A cast was applied and the patient was given sulfanilamide. His temperature fell to normal on the 16th day. The wound was entirely healed in 2½ months after operation. He was allowed to bear weight a week later. The roentgenogram of March 31, 1937 shows very definite distention of the capsule with no definite evidence of any involvement of the upper tibial or lower femoral metaphysis. That of June 25, 1937 still shows capsular distention and thickening. Those of June 20, 1940 show definite healing with a wide joint space and little or no disturbance of the femoral epiphysis. His latest follow-up, 3 years after operation, shows no lump, a full range of motion in his leg, and the left leg is ¼ inch longer than the normal leg. This is a very fortunate outcome in acute streptococcus arthritis of the knee joint in an infant.



Case 2—R H, St. Luke's No. A 6792, male, 8 years of age. He was admitted to St. Luke's Hospital December 9, 1938, 2 weeks after pain began in the left knee. He had no history of trauma or previous infection. Temperature was 104 degrees and white blood cells 14,400. Blood culture showed hemolytic staphylococcus. On December 19, 1938, an incision and drainage of the lower femoral metaphysis was performed through a trap cut in the bone. A plaster-of-Paris dressing was applied. He remained 54 days in St. Luke's Hospital. He was entirely healed in 4 months. The roentgenograms of December 10, 1938, antero-posterior and lateral, show involvement of the lower femoral metaphysis. The roentgenogram of January, 1939, shows the trap which has been removed from the femur, and those of September, 1940, show healing of the lesion. In September, 1940, nearly 2 years after onset, he has a full range of motion in his knee joint and hip joint, and his legs are of equal length. He has no additional focus. To date this has been a perfect result. This is a single lesion with a single operation and he is healed without disability.



Case 3—C W, St Luke's No 107-038, male, 56 years of age. Following a prostatectomy, October 1, 1933, the patient ran a high temperature with localized infections, abscesses on his arm, phlebitis of the leg, etc. Blood culture was positive, *Streptococcus angiosus*. Within a month he began to complain of pain and stiffness in the small of the back, and by March, 1934 these "lumbago" pains had become very acute. The x-rays of the spine taken in March, 1934 showed a definite destructive lesion in the first and second lumbar vertebrae. His pain continued and by the latter part of November he had developed a large right psoas abscess which was incised and drained at St Luke's Hospital. Following the operation a tiny sinus continued to discharge for 8 to 9 months and then healed. The lateral roentgenogram of the lumbar spine of March, 1934 shows a definite suppurative disease of the first and second lumbar vertebrae. The roentgenograms of October, 1934, antero-posterior and lateral, show progressive involvement of these two vertebrae with an enormous psoas abscess. The roentgenograms of March, 1938, lateral view, shows healing with some spontaneous fusion of the involved vertebrae.



Case 4—L. B., St. Luke's No 111-080, male, 14 years of age. This patient gave a history of severe pain in the left knee with marked swelling and high fever following a long horseback ride. He was seen by two physicians who made a diagnosis of acute rheumatic fever. The patient had a systolic heart murmur. I saw the patient when his symptoms were subsiding and he was in his home without x-rays. I asked to have these taken but for some reason they were not taken. The patient within a month had a very nearly complete range of motion in his left knee. The first roentgenograms taken in February, 1926, 5 months later, showed very definitely that the patient had had an acute suppurative osteomyelitis of his femur. From 1925 through 1935 the patient has had about 10 small abscesses which have been incised and a number of small sequestra have been removed from the superficial tissues. This patient has played football and hockey all the way through college, and when last seen, 15 years after onset, he was healed. He had a full range of motion in his knee joint, and there has been no growth disturbance. The roentgenogram of February 21, 1926, shows rather massive involvement of the lower metaphysis of the left femur, and the roentgenogram of June, 1934 shows marked recalcification and healing with apparently one or two sequestra still in the femur. This patient is shown because of his original diagnosis of acute rheumatic fever, an error which, fortunately, was not disastrous.



Case 5—K C, St Luke's No A 01784, male, 8 years of age. He was admitted to St Luke's Hospital June 22, 1936. The patient had a sty 2 weeks prior to admission and 4 days prior he developed pain in his right hip. He showed marked pain, tenderness and spasm in the hip joint. His temperature was 104 degrees and white blood cells 13,186. Blood culture was positive, hemolytic staphylococcus aureus. The hip joint was aspirated and a large amount of thick yellow pus evacuated. An incision and drainage was done with drill holes in the neck of the femur. A plaster-of-Paris spica was applied. Culture of the pus showed hemolytic staphylococcus aureus. A sequestrectomy was done on October 5, 1936, incision and drainage on April 16, 1938, hip fusion on October 28, 1938, and incision and drainage on December 22, 1938. The roentgenogram of June 12, 1936 shows no evidence of involvement of the upper femoral metaphysis. The roentgenogram of September 18, 1936 shows very definite

involvement of the upper femoral metaphysis, a small sequestrum and marked thinning of the hip joint space. The final roentgenogram, September 3, 1940, shows the hip joint solidly fused in excellent position, no evidence of any sequestrum. There is no evidence of atrophy. This patient has been bearing weight quite steadily and is now healed.

THE PREVENTION AND TREATMENT OF INFECTION IN WOUNDS BOTH OPERATIVE AND ACCIDENTAL*

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INTRODUCTION

THE title of this paper calls for a discussion of rather wide scope dealing with two more or less distinct and fairly complicated problems, namely, infection in operative and in accidental wounds, and yet they are related and in some respects they run parallel with one another. In both, of course, we are dealing with wounds contaminated with bacteria. On the one hand, we have built up an elaborate system fairly generally followed throughout the so-called civilized world, called "sterile technique," designed as a prophylactic against operative wound infection. On the other hand, not anticipating accidents, no effort is made to prevent bacteria from gaining admission into the tissues at the time of an accident. The prophylaxis is directed at preventing those organisms from gaining a foothold in the body after they have entered the wound.

Operative wounds occur in both normal and debilitated individuals with the latter probably outnumbering the former. Accidental wounds occur more often in healthy rather than debilitated people. In operative wounds there is, or should be, relatively little trauma to the tissues but the wound is exposed to contamination for a relatively long time. In accidental wounds there is frequently extensive trauma to the tissues but there may be only a brief period during which organisms enter the wound. In operative wounds under ideal conditions the organisms which are introduced are few in number and of low virulence. In accidental wounds the organisms which get in are many and may be of high virulence. In operative wounds the foreign bodies which are introduced are for the most part sterile. In accidental wounds the foreign bodies are

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usually highly contaminated. Operative wounds occur when the various physiological processes of the body are being considerably disturbed, circulation, alimentation, respiration, urination, fluid, protein and electrolyte balance, and so forth. Accidental wounds occur when most of the body functions are normal. Both operative and accidental wounds are frequently accompanied by varying degrees of shock or hemorrhage or both. All of these things have some bearing on the development of wound infection and on the measures we may take to prevent or treat such infections. In the case of operative wounds the surgeon has the situation more or less under his control from beginning to end and the percentage of infections is low with a comparatively low death rate. With accidental wounds the surgeon can only begin to control the situation after the patient comes to him and any delay generally increases the incidence of infection and raises the death rate.

The question which we have to face this evening is, how can operative wound infection be brought down to the irreducible minimum and how can the incidence of accidental wound infection approach this same figure? In other words, can we further control the development of operative wound infection? Is there any way to bring accidental wounds under prompter and better control? This paper will endeavor to present the pros and cons of these two questions.

OPERATIVE WOUND INFECTIONS

Recent reports in the medical literature indicate that this important problem is being studied by a number of individuals in different clinics. In almost every instance such a study is initiated because of some catastrophe or some unexpected incidence of wound infection and each author emphasizes one or another factor in the problem, often to the exclusion from consideration of the other factors.

Every hospital has its own rules for sterile technique and these are largely based on a few fundamental principles laid down by Pasteur and Lister sixty or more years ago. Before that time it was fully expected that every operative wound would become infected. After that time postoperative infections began to disappear until now we expect operative wounds in clean cases to heal without infection. Sterile technique that is handed down from generation to generation by staff surgeons or surgical residents frequently becomes modified from year to year either consciously or unconsciously. The occurrence of an unexpected wound

infection may arouse the surgeon to seek some explanation for the incident in that individual case or it may cause him to check up every step in the sterile technique in his own hospital. This may even lead to some experimental studies in those fields where perfect sterility has not yet been obtained. Wherever such a study is first started, the incidence of infection is usually found to be high but if the study goes on and the interest of the staff is maintained, the incidence goes down even if the weak spots in the technique can not be definitely proven. The staff becomes "wound infection conscious," little breaks in technique are promptly noticed and corrected and the doors through which contamination may come are gradually closed.

CONTAMINATION OF THE WOUND

What are the principal sources of bacterial contamination of operative wounds? We can look at this question from two points of view to find the answer. First, we can determine what organisms are found on culture when an infection develops and search the operative surroundings for similar organisms. Secondly, we must consider everything which comes in contact with the sterile field to be a potential carrier of organisms.

In a large series of postoperative infections it is found that *Staphylococcus albus* is the most common organism. This is usually associated with the mild or trivial infections. In the serious infections we find the *Staphylococcus aureus* and the hemolytic streptococcus, the non-hemolytic streptococcus, the *Bacillus coli*, and more rarely the *Bacillus pyocyaneus*, anaerobic streptococcus and *Clostridium welchii*. Where are these organisms found in the neighborhood of the operative field? First of all, the skin of the patient, of course, may have on its surface any organism, but even when it has been thoroughly washed with soap and water, ether and alcohol and painted with an antiseptic, if bits of skin are taken for culture, the *Staphylococcus albus* is almost invariably found and occasionally the yellow staphylococcus. No skin antiseptic has yet been found which will penetrate the pores of the skin sufficiently to destroy all of the organisms harbored there. However such cleansing should be done and skin antiseptics should be used to bring down the number of organisms to a minimum. Tincture of iodine has been time honored as a skin antiseptic and although others have been recommended and are frequently used in our researches they

have fallen short of iodine in the percentage of negative cultures when bits of skin are taken for culture. This is one vulnerable spot in our sterile technique and one which should be strengthened. After the incision is made towels clipped to the skin edges will minimize the entrance of organisms discharged from the pores to the surface of the skin during the course of an operation.

But where do the hemolytic staphylococci and hemolytic streptococci come from that are found in the more serious operative wound infections? The chief source of these is unquestionably the noses and mouths of the people in the operating room. Coming as they do from a condition of active growth in a human environment, if they are discharged directly into the wound from the unmasked nose of any member of the operating team, they find themselves in a favorable environment similar to that from which they came and they lose no time in continuing their rapid multiplication. These organisms are no respectors of persons, they lodge in the noses and throats of the professors of surgery as well as the junior member of the team, the nurses, anesthetists, orderlies and the visitors who so frequently peer over the shoulders of the operators. There is no excuse whatsoever for anyone entering an operating room either during an operation or at any other time without adequate masking of both the nose and throat. It was proven beyond the shadow of a doubt by culture and by cross absorption of agglutinin tests that a hemolytic streptococcus causing a serious wound infection in a patient was identical with a hemolytic streptococcus harbored in the unmasked nose of the sterile nurse who was on the operating team when the operation was performed.¹

Now what is an adequate mask? A four ply fine meshed muslin gauze will catch the droplets but some organisms not contained in droplets may pass through or around such a mask. An impermeable mask, with a rubber, cellophane or paper membrane incorporated in the gauze will prevent the direct passage but will increase the number of organisms which are carried around the impermeable layer. Such masks may be incorporated into a helmet of fine meshed gauze which can extend down into the sterile gown. Such a mask will not only prevent particles falling from the hair or neck of the operator but will divert air currents down into the gown. It may feel a little uncomfortable when first worn but habitual use will soon make the wearer unaware of it and it will reduce contamination from this source to a minimum. The perfect mask which

will stop completely all organisms from this source has not yet been found. Further precaution should be taken by any operator to minimize conversation during an operation, for unquestionably more organisms are cast out during speech than during quiet breathing.

The hands of the members of the operating team may be another source of virulent hemolytic staphylococci or streptococci or the intestinal organisms including the "gas bacillus," particularly if they have recently dressed patients with such infections. These organisms may be transferred to the hands by handkerchiefs from the individual's own nose and throat. Scrubbing hands with scrub brush and soap under running water will remove the great majority of these organisms if the scrubbing is done thoroughly and systematically, going over the whole surface of hands and forearms and elbows with particular care to remove dirt from beneath the finger nails. Five minutes of vigorous scrubbing should be enough, a longer period may do damage by abrading the skin. An additional protection is given by covering hands and arms and cleaning under nails with a suspension of lime and soda left on for 2 to 3 minutes and then washed off with 70 per cent (by weight) alcohol. But these hands should not be considered sterile. They should be powdered before the gown is put on. Stockinette sleeves will rub off the excess powder which might fall down upon sterile gloves or on the sleeves of the gown. Gloves are then held open by the sterile nurse in such a manner that the hand can be inserted without touching the edge, for this can not be done by the operator himself with the newer anode process gloves. It can be done, however, with the older gauntlet ribbed gloves, which may be put on by the sterile nurse who is the first to scrub and then discarded after she has held the gloves of the other members of the team, one of whom may then hold fresh gloves for her. Thus may the organisms from this source be reduced to a minimum. If any gloves are torn or pierced during an operation they must, of course, be changed at once.

Another obvious source of contaminating organisms is the air. Dust particles and suspended moisture particles contain them. They are carried around the room by air currents and fall on the sterile field and sometimes directly into the wound. Culture plates placed in various parts of the room have demonstrated that anywhere from 30,000 to 60,000 viable organisms descend upon a sterile field during the course of an hour's operation.² Only one tenth of this number is found on plates

exposed in an empty operating room before an operation, but the number rapidly rises as soon as people come in and move around depositing organisms from their shoes and clothing. It is obvious therefore that the number of persons entering the operating room should be reduced to a minimum and they should wear sterile gowns and shoe covers. Their movements about the room should be limited and the opening and closing of doors should be cut down as much as possible. The deposit of these organisms on the sterile field may be further minimized by the use of canopies over sterile tables.

In the last few years attempts have been made to destroy these organisms by means of ultraviolet radiation. There are zones in the ultraviolet spectrum where the rays are highly bactericidal with a minimum of erythema producing effect and such zones may be selected by using the proper kind of glass for the tubes. Hart³ has presented evidence to show that ultraviolet radiation may completely destroy air organisms with intensities not injurious to tissues. He has also shown that the incidence of infection in operative wounds in cases operated upon under these rays, is considerably reduced as compared with a previous control series. Furthermore, the postoperative temperature curves in such patients are lower than in control cases even without infection. In our laboratory Kraissl⁴ with the technical assistance of engineers from the Westinghouse Company has devised a series of ultraviolet tubes incorporated in a circular illuminating unit with a central vent. The heat of the lamp causes convection currents to ascend through the lamp and carry the bacteria laden particles past the most intense focus of the ultraviolet rays which is about a foot above the wound. Such tubes emit rays in the bactericidal zone with intensities sufficient to kill the great majority of suspended bacteria over the sterile field. Independent wall units are employed to cover the areas surrounding the operating table. The intensities used are within the safety zone as far as injury to the tissues go and the intensity may be automatically reduced during the course of the operation, while it may be stepped up as the tubes begin to show evidence of losing some of their strength in the course of time. We have had such an installation in one of the operating rooms at the Presbyterian Hospital for the past few months and are ready to make a preliminary report to the effect that all clean operations which have been performed under it have resulted in clean wound healing without exception. "Clean-contaminated" wounds in regions which are uninfamed at the time of

operation but which become contaminated by bacteria from neighboring tissues during and after operation have shown a much lower incidence of wound infection than control series. We have not been able to completely sterilize the air with intensities which we consider safe but we have reduced the number to approximately 10 per cent and the wound healing figures, although it is a small series, seem to be significant, and warrant the continued use of this additional safeguard.

With regard to catgut and the ligature and suture material, conditions have greatly improved in the last ten years. Now, the new Pure Food and Drugs Act has defined as drugs, catgut and other suture material as well as cotton, gauze bandages and all materials sold as sterile goods. The Food and Drugs Administration of the Department of Agriculture has been given responsibility for setting up a continuous control by means of the periodic examination of goods bought on the open market and by the confiscation of goods not meeting the standards. The United States Pharmacopoeia with the help of a "Sterile Products Advisory Board" has set up standards and stipulated certain tests for sterility. These standards will begin to operate on January 1, 1941, and it is hoped that unsterile catgut will disappear from the market forever.⁵

This brings us to the last category, namely, the instruments and utensils, the linen goods, the cotton, the gauze, the sponges, the compresses, towels and sheets, namely, everything which goes into and comes out of the water sterilizers and the autoclaves. Everything that has gone before must be considered contaminated in spite of all of our efforts to reduce the contamination to a minimum. Instruments and dry goods can be and should be made absolutely sterile. But I am sorry to say they are not always sterile, either because of faulty apparatus or the faulty use of good apparatus. With regard to the instrument and utensil sterilizers, precautions must be taken with the plumbing to use traps in the drainage pipes which will prevent the reflux of sewage water at the end of sterilization. Ten minute boiling will destroy all known pathogenic organisms. Although some non-pathogenic spores have been found which will survive boiling for an hour they need not be considered. This ten minute period must not be shortened to please an impatient surgeon calling for an instrument which was not ready. Walter has devised a rapid autoclave for instruments in which they are washed and sterilized at the same time in a much shorter period of time.⁶

Sharp instruments like knife blades, scissors and needles, which be-

come blunt by boiling, can be sterilized in 15 to 20 minutes by soaking in Bard-Parker germicide or its equivalent

The autoclaves should have both pressure and temperature gauges with self-recording mechanisms and charts. There should be a stop cock to let out the air at the bottom of the chamber during sterilization. Doubly wrapped packages should be prepared and drums should be loosely packed so that air pockets will not be retained within them. Gloves should not be folded or placed in the autoclave with fingers down for fear that air may be pocketed in finger tips. Similar objects should be so packed that the air may be displaced downward out of them as the steam enters. An important safeguard is the preliminary evacuation of air with a vacuum of minus 10 cm of mercury for 15 minutes. We have found that if this is done the sterilizing time may be shortened to 30 minutes, although 45 minutes gives a wider margin of safety. Without the vacuum, sterilization may not be effected for an hour or more.² Commercial indicators are not reliable to demonstrate that sterilization has been satisfactorily accomplished. Resistant spores of non-pathogenic organisms (*B subtilis* or *B sporogenes*) incorporated in cotton threads and doubly wrapped in muslin should be employed as indicators. They should be placed in a package near the air vent and sent to the laboratory for culture when the autoclaves are opened. With such precautions and with conscientious technicians I believe that we should be sure of absolute sterility in our autoclaved materials.

CONTAMINATION OF OTHER TISSUES

We have so far considered the sources of bacterial contamination of the wound at the time of operation. We must also consider briefly the contamination of other regions in the patient during and just after operation. First of all, the respiratory tract during anesthesia becomes contaminated by mouth organisms ordinarily discharged by the normal functioning of the cough reflex. These organisms frequently establish themselves in the lungs and cause a postoperative pneumonia. This contamination may be minimized by retaining the cough reflex whenever possible and by the suction of any excess of mucus during the course of anesthesia. Occasionally during the induction, but more often at the end of anesthesia the patient vomits and aspirates this material. This is a frequent cause of the more serious forms of pneumonia and occasionally results in lung abscess. The withholding of food before operation

and the usual precautions during these phases of anesthesia should minimize the occurrence of this accident. If vomiting does occur a dependent position of the head, suction and the returning cough reflex may prevent too much aspiration.

If voiding is impossible and catheterization has to be resorted to, organisms are almost invariably introduced into the bladder because of the impossibility of sterilizing the urethra. Infection should not occur unless catheterization is repeated many times and the bladder is permitted to distend unduly or not empty completely.

Hypodermic and intramuscular injections which are frequent after operations are occasionally the agents of infection if the proper precautions are not taken to sterilize syringe and needle and the skin at the site of injection.

THE ESTABLISHMENT OF INFECTION

The development of an infection within the body depends not only upon the introduction of organisms into the tissues but upon the local conditions within those tissues and in the body as a whole which favor or retard the establishment of colonization of these organisms. In certain animals and probably in humans, the introduction of a single virulent organism may result in an infection and death. On the other hand the introduction of millions of less virulent organisms may produce no infection whatever. The outcome depends upon the relative strength of the offensive forces of the organisms and the defensive forces of the body.⁷

Certain measures may be taken by the operator to minimize the development of infection in a wound which becomes contaminated under our so-called sterile technique. The most important of these is minimizing trauma. Sharp cutting should be used in making incisions and dissections, retraction should be gentle, artery clamps should not seize masses of tissue. Hemostasis should be complete. Fine silk should be used for ligatures and sutures in all clean cases. Since 1930, when we began silk technique in steadily increasing numbers of clean cases, every year has demonstrated a lower incidence of infection with silk as compared with catgut. If there is an established infection or gross contamination fine catgut should be employed—never heavier than size 0. The maximum blood supply should be conserved. No tension should be used which will cut off blood supply. All old blood and cellular debris should

WOUND HEALING—CLEAN CASES 1925-1939

Year	Cases	Percentage		
		Total Inf	Triv Inf	Ser Inf
1925	558	14.0%	10.0%	4.0%
1926	581	15.0	11.0	4.0
1927	653	15.0	12.0	3.0
1928	640	11.0	9.0	2.0
1929	771	9.0	7.0	2.0
1930	747	10.0	7.0	3.0
1931	950	7.1	5.4	1.7
1932	1053	5.3	4.2	1.1
1933	1132	4.8	3.6	1.1
1934	1279	3.7	2.8	.9
1935	1417	3.1	2.5	.6
1936	1558	3.1	2.5	.6
1937	1614	2.2	1.4	.8
1938	1668	2.1	1.6	.5
1939	1725	2.6	2.0	.6

be washed out of the wound before final closure. Ether may be used for this purpose. Before closure, the introduction of potent staphylococcus bacteriophage or sulfanilimide powder has been advocated but with the incidence of infection already low with the above precautions, these procedures are not at present advisable. A continuous study of wound infections is of great importance in reducing the incidence. It keeps the staff "infection conscious." Everyone tries to lower the figure and weak spots in the technique are strengthened. Our figures for the last 15 years bear this out.

CLEAN-CONTAMINATED CASES

So far we have been speaking of the prophylaxis of wound infection in clean cases. There is another large group of operative cases in which there is no established infection but the wound becomes contaminated immediately because of our inability to sterilize the surface, even approximately, or because of the proximity of contaminated regions, or because the operative incision passes through normal tissues into an infected cavity or viscus. Such operations are those performed on or near the mouth or the vagina or rectum. In this group are acute appendicitis cases which are not drained, all gallbladder, stomach and intestinal

operations In this group also we have included accidental wounds, such as compound fractures, in which the region has been contaminated and an operative procedure is necessary We call these cases "clean contaminated" and do not expect as perfect wound healing as in clean cases For example, in 1939 we had a total of 2.6 per cent of infections in 1725 clean cases Of these 0.6 per cent were serious In the same year we had a total of 8.7 per cent of infections in 866 clean contaminated cases of which 2.1 per cent were serious In the prophylactic treatment of these wound infections all of the measures which we use in clean cases should apply In certain cases drains should be used In heavily contaminated cases the skin and subcutaneous tissues should be left open But in this group we have an added responsibility We must try to prevent the growth of organisms which we know have grossly contaminated the wounds Zinc peroxide should be applied where anaerobic organisms are known to be involved, as around or in the mouth, or around ostomies of the large bowel, or around the anus, or in the vagina after perineoplasties, and after perineal resections, hemorrhoids, fistulae and pilonidal cysts As a prophylactic against infection of the peritoneal cavity after appendectomy or abdominal resections of the bowel, Steinberg⁵ has advocated in recent years the use of rapid vaccination of the cavity with colon bacilli suspended in gum tragacanth This has yielded favorable results in reported cases but more recently the use of the sulfonamide group of drugs has been so encouraging in the hands of Lockwood and Ravdin⁶ and others including our own clinical and laboratory experiences not yet reported, that they warrant further clinical trial and if possible extensive experimental investigation Particularly encouraging in compound fractures are the results in two fairly large series of cases in Baltimore treated by Bennett and Long¹⁰ with general sulfanilamide and in Minneapolis by Jensen and his co-workers¹¹ with local application of the drug The lack of adequate bacteriology in these series makes it uncertain just what organisms responded favorably and which failed to respond, but gas gangrene was absent in all of these cases In a smaller series of 18 compound fractures treated by Pulaski, 15 were left open and dressed with zinc peroxide without an infection Three were closed and became infected These wounds were opened and were treated with zinc peroxide and the infection ceased A control series of 19 patients treated during the same period had 5 infections, including 1 case of gas gangrene developing in a stump closed after amputation This small

series suggests that this drug also may be effective in preventing infection in compound fractures. Further extensive clinical trial checked by adequate laboratory work will have to be done before these newer methods can be properly evaluated.

ACCIDENTAL WOUNDS

An accidental break in the surface covering of the body carries into the wound organisms which were on the surface and others which were on the object causing the wound. Frequently also street dirt or garden soil or clothing are carried in, bearing bacteria and in some instances chemicals more or less irritating. Such wounds occur usually in healthy individuals who are moving around and bumping into other people and things. Not infrequently a fist crashes into a set of teeth with disastrous results.

In industry, to be sure, safeguards are placed on machinery to minimize accidents. Frequent washing of hands is encouraged to reduce the entrance of bacteria and dirt if accidents occur, but accidents are never really expected and, so far as I know, no serious effort is made to prevent organisms from getting into a wound primarily at the time of accident. Of course, secondary contamination is another matter. Thoughtless individuals may wipe away the blood with an unsterile cloth, or an article of clothing, or they may suck the wound or they may apply some household remedy and thus secondarily contaminate the wound.

Accidental wounds may range from a tiny pin prick or scratch which does not draw blood to an extensively comminuted fracture with extremely damaged muscle. Minor wounds are usually cared for by the patient himself until the wound is healed or until an infection gains a foothold when he may put himself in the hands of a doctor. With major wounds, particularly those with much loss of blood or functional disability, the patient goes promptly to the doctor. In industrial groups with medical supervision, the injured man goes to the doctor for the most trivial as well as the most serious injury. Thus, the surgeon has an opportunity to use all of his knowledge and ingenuity to prevent further injury, eliminate the threat of infection and favor rapid healing with restoration of form and function. What should the surgeon do when an injured patient comes under his care? He must assume that all accidental wounds are contaminated. He must try to anticipate what organ-

isms are present in order to give the best primary treatment and he must know as soon as possible exactly what organisms he has to deal with. To be specific let us say that a nurse has pricked her finger with a pin while dressing a patient. The surgeon finds out the nature of the patient's infection—a hemolytic streptococcus empyema. He knows that any medication applied locally will not reach any inoculated organisms. Shall he cut out the wound or be conservative? I believe that he may safely be conservative, depending upon sulfanilamide to fortify the patient against infection, even if the inoculation has entered a tendon sheath. Soaking the finger at frequent intervals in water at 110° F will favor resolution of the process. But the surgeon must watch for the earliest indication of inflammation and if it develops be ready to go in and establish drainage.

An easier decision may be made when the accidental wound is a laceration of the soft parts following a street accident. In this situation the intelligent surgeon must anticipate the presence of anaerobic organisms including tetanus and gas gangrene. Immediate operation is required. The patient is prepared under regional block or general anesthesia. If there has been considerable bleeding a tourniquet should be applied but not left on for more than 20 minutes for the upper extremity, or 40 minutes for the lower extremity, without being released. The wound is then protected by gauze while the neighboring skin is thoroughly cleaned with soap and water or benzene followed by ether and 70 per cent alcohol. The margins and surfaces of the wound should then be cut away leaving grossly normal tissues on all surfaces. All foreign bodies must be removed. (All of the debrided tissue and foreign bodies should be taken in a sterile receptacle to the bacteriological laboratory for a complete bacterial analysis by aerobic and anaerobic methods.) I cannot too strongly impress upon you the importance of this. If any tendons or nerves have been severed they should be carefully approximated with fine silk. Hemostasis should be complete—catgut ligatures should be applied to vessels so as to include only a minimal amount of the surrounding tissue. After debridement the wound should be irrigated with large quantities of normal saline.

Now the question arises, shall the wound be closed with or without drainage or shall it be left open? If the operation is done within 6 hours of the time of the accident, the surgeon will have to use his own judgment based upon his knowledge of the conditions of the accident, the

age and general health of the patient, the degree of tissue damage and the extent of the debridement. The wound may be closed without drainage if it is dry and shallow. A small Penrose tube should be inserted if it is deep or moist. A thin layer of sulfanilamide powder may be laid over the wound surfaces before their approximation. If this is done, drainage should not be used. Sulfanilamide should also be given systemically. The patient should be tested for serum sensitivity and if he is not sensitive, he should receive 3000 units of tetanus antitoxin and one therapeutic dose of polyvalent anti-gas gangrene serum. In 24 hours the cultures should reveal most, if not all, of the organisms with which one has to deal. A closed wound puts a burden of responsibility upon the surgeon, for he must watch carefully for the first evidences of infection and if they appear, he must decide by the severity of the signs and the nature of the organisms whether or not to open the wound again. If a *Staphylococcus albus* is present, the wound may be left closed unless the signs become pronounced. If a *Staphylococcus aureus* is present, the wound should be opened if more than minimal signs develop. Potent bacteriophage will help to control the infection. If a hemolytic streptococcus is present, the wound may be left closed unless signs become marked. If anaerobic streptococci or Welch bacilli are present, the wound should be opened and zinc peroxide applied^{12, 13}. If there is a mixture of organisms present, there is still greater indication than for a single species for opening a wound which has been primarily closed.

If the debridement is done more than 6 hours following the accident, sulfanilamide should be given systemically and the wound should be left open. Then the surgeon must decide what to apply as a dressing—fine meshed vaseline gauze to be left without change or sulfanilamide powder or zinc peroxide. We do not know as yet what is best. This question should to be subjected to an extensive clinical experiment carried on in several different hospitals. For the present I would personally prefer zinc peroxide for the first dressing until the cultures are heard from, because of the frequency of anaerobic contamination in accidental wounds. If no anaerobes or hemolytic streptococci are found, it may be discontinued and vaseline gauze or China silk with normal saline applied. If staphylococci are found, I would test them for susceptibility to a potent bacteriophage and apply that on China silk once or twice daily. If hemolytic streptococci are found, I would either continue zinc peroxide or change to sulfanilamide. If *E. coli* or a mixture of aerobes are present,

sulfanilamide is the dressing of choice, although a potent phage might be more effective against the colon bacillus

In the treatment of compound fractures there seems to be a difference of opinion at present and this question likewise should be subjected to a well controlled clinical and bacteriological study I have already referred to the work of Bennett, Jensen and Pulaski in speaking of clean-contaminated wounds

Trueta's method of treating compound fractures, which he used in Spain, has stimulated wide interest and its favorable results have been reported from England¹⁴ He practiced extensive debridement of the wound and applied dry gauze dressing and fixation in plaster without a change of dressings for several weeks In over 1000 cases only 8 per cent became infected with one case of gas gangrene and only one death—a truly remarkable series The end results of this treatment have not yet been reported but from a primary infection standpoint it is extremely encouraging Whether these figures can be improved by the administration of sulfanilamide or zinc peroxide locally before closure or sulfanilamide by mouth will not be known until they have been tried in comparable series

It seems probable that in civil practice the best results would be obtained by wide debridement, internal fixation, open wound, sulfanilamide by mouth and either zinc peroxide or sulfanilamide locally

THE ACTIVE TREATMENT OF INFECTIONS

The Active Treatment of Postoperative Infections If, in spite of all of the precautions of sterile operating room technique, a wound infection develops, active treatment to combat the infection is called for One can tell from the local reaction as well as the general symptoms whether the infection is trivial or serious If it is trivial, local treatment is all that is necessary The involved portion of the wound must be opened and the pus evacuated Deep pockets may require drainage Cultures must be taken and appropriate specific treatment may be instituted In the serious cases of wound infection something more active is required in the way of treatment These infections usually occur in the first few days after operation An unexpected temperature always requires an examination of the wound Sometimes pulmonary signs and symptoms divert the attention and the surgeon may fail to appreciate that the wound is the cause for major concern This is particularly

likely to occur when gas gangrene is present, giving alarming general symptoms. Usually, however, local pain calls attention to the wound. If there are signs of inflammation—swelling, redness, tenderness or crepitus—the wound should be opened to the full extent of the involved portion. A smear of the pus should be stained at once, for the morphology of the contained organisms may reveal their nature. Presumptive diagnosis by smear should, of course, be confirmed by culture. This may change the initial procedure, but treatment should be started at once and should be as specific as possible. If the organism is a staphylococcus and a potent bacteriophage is available, it should be applied daily to all parts of the wound surfaces. If it is an odorless streptococcus, probably hemolytic, sulfanilamide should be used both generally and locally.

If large Gram-positive rods are numerous, the Welch bacillus may be assumed. Further evidence of this are gas bubbles in the exudate, necrosis of the muscle and crepitation, either felt with the hand or heard with the stethoscope. The exudate may have a "mousey" odor and the skin may show slight bronzing. Such a wound should not only be opened widely but all necrotic tissue should be cut away until normal tissues are reached. Then the wound should be flooded with a suspension of zinc peroxide, the surfaces covered with a thin layer of absorbent gauze soaked in the same suspension and overlaid with cotton soaked in water—the whole dressing then sealed with vaseline gauze.

In suspected gas gangrene cases no time should be lost by waiting for the report on the culture, polyvalent gas gangrene serum should be employed, three "therapeutic" doses to start with and continuing with one therapeutic dose every 6 to 8 hours until a fall in temperature has taken place and there is some evidence of lessened toxicity. On the basis of certain encouraging clinical observations sulfanilamide may also be given by mouth in cases of gas gangrene. The actual benefit reported may be due to the effect on associated organisms, because in pure culture in experimental animals benefit from sulfanilamide therapy has not been surely demonstrated. X-ray therapy in three or more doses of 50 r has been advocated and a striking lowering of mortality has been reported.¹⁵ We can not as yet advise treating such cases with x-ray without further evidence, for its exponent says that if x-ray is employed, sulfanilamide, serum and even surgery are all contraindicated.

Streptococci by smear and a foul odor from the exudate suggest anaerobic streptococci. These are often associated with spirochaetes and

fusiform bacilli or with Gram-negative bacilli either aerobic or anaerobic. In all such cases zinc peroxide applied locally as above described is the treatment of choice and again it may be supplemented by sulfanilamide by mouth until we know more definitely the indications for and the limitations of these sulfonamide drugs.

If an infection of any nature becomes localized and there is much slough, hypochlorite solution should be used to favor its liquefaction, either as two-hourly dressings with changes of fine meshed gauze or cotton or delivered at frequent intervals by means of a tube.

In a small percentage of postoperative wound infections a septicemia develops, the organisms usually being the hemolytic streptococcus or the *Staphylococcus aureus*. In the former situation, sulfanilamide treatment should be vigorously pursued with careful daily studies of blood levels, blood counts and blood cultures. Transfusions have been successfully employed when donors could be obtained whose blood showed a high opsonic index for the infecting organism.¹⁶

If the organism is a staphylococcus the drug of choice is sulfathiazole with the same careful observation of laboratory studies. But staphylococcus septicemia cases should have the benefit of doubly potent staphylococcus bacteriophage and its administration should not be withheld to see what the drug will do alone. It should be given in slowly increasing doses from 0.25 to 5 cc, diluted ten times in saline, at hourly intervals for the first 8 hours and then in doses increasing more rapidly in 5 cc increments every 4 to 8 hours until the patient is receiving 75 cc a day. If no improvement is seen in 3 days and there is no reaction, the dose should be further increased up to 150 cc a day.¹⁷

In both hemolytic streptococcus and *Staphylococcus aureus* septicemia, the distributing focus should be found and appropriately treated surgically by incision or excision. Metastatic foci should be watched for daily and drained if localizing signs are present. Bacteriophage and the sulfonamide drugs certainly help to prevent these metastatic lesions but if they develop we have definite proof that bacteria have gained a foothold in spite of them and these foci must almost always be drained surgically. Otherwise, they will in turn become distributing foci.

In most cases, postoperative wound infection comes under control within a few days. However, the average stay in the hospital for an infected case is double that of a corresponding clean case. This is of considerable economic importance to both the patient and the hospital.

Furthermore, wound infection may completely nullify the operation, for example, an infected hernia very frequently recurs and has to be repaired again. In a few cases death ensues, but this is fortunately rare.

Postoperative pneumonia has in the past usually been relatively mild and not a serious complication. The organism is usually a pneumococcus of one of the higher numbered types. The temperature often goes up on the first or second day after operation and it may come down spontaneously in two more days. A plug of mucus may close off a bronchus and an atelectasis form with a relatively minor role played by the infection. Other cases have a more difficult time with continued fever, severe cough with purulent sputum and occasionally empyema and lung abscess or wound disruption. Postoperative pneumonia usually responds well to sulfapyridine or sulfathiazole. It is often necessary to give the sodium salt of either drug intravenously because of the necessity for withholding everything from the stomach. It has been observed that the pyridine derivative will last longer in the blood than the sodium sulfathiazole but it is more nauseating and the nausea lasts longer (4 to 5 days) than with thiazole (12 to 24 hours). Therefore, it should be given with great caution to the patient whose stomach is upset by the operative procedure itself and patients in whom repeated vomiting puts an undue strain upon the wound. Luminal helps to minimize this nausea. As in medical pneumonia the drug should be continued for several days after the fever has subsided.

Urinary infections which develop following catheterization usually yield *E. coli* or non-hemolytic streptococci and occasionally both together. Sulfathiazole is the drug of choice, if the patient's kidneys are normal, for it is rapidly excreted through the urinary tract. In pure *E. coli* infections a potent bacteriophage may clear up a cystitis or a pyelitis if it is given intravenously as well as locally.

The Active Treatment of Infection in Accidental Wounds If infection becomes established in accidental wounds in spite of the prophylactic measures which have been employed, the methods must be changed to meet the new situation. This should be based entirely upon the results of the bacteriological study of the debrided tissue and secondary cultures from the now infected wound. The former culture will show the potential factors of infection. The latter culture will show what organisms have survived and gained a foothold in spite of the measures which the surgeon thought would ^{be adequate} at the time of

the first operation

I have indicated above in discussing the treatment of operative wound infection the measures required for specific types of infection. The same rules apply to the established infections in accidental wounds. The general principles involved are three in number. One must be sure of, 1 adequate exposure of the infected tissue, 2 adequate contact between the infected surfaces and any local medication, and 3 adequate dosage of internal medication.

Adequate exposure of infected tissue may be obtained by the removal of any suture used to close the wound, or it may mean further incision. This should be carried to the limits of the involved area with a comfortable margin. It is better to do too much than too little. I do not fear the spread of infection as a result of extending the incision through the barrier which has been built up. If no attempt is made to close such incisions, any unnecessary incisions or any unnecessary part of an incision will be the first to heal.

Adequate contact with local medication is of great importance. If there are any nooks and crannies in the wound where the medication does not touch, the organisms may escape its action. Bacteriophage being fluid may run everywhere in the wound but it may run out again if it is not held in contact with gauze or cotton. Sulfanilamide must go into solution in the tissue juices before it can have any effect but if the wound is closed it is rapidly absorbed in 3 to 4 days, and if the wound is open, it will run out unless held in place. It may be best applied to the wound surface by means of a powder atomizer. Zinc peroxide acts best if it is kept wet. Tissue fluids will activate it but distilled water or 2 per cent polyvinyl alcohol will keep it wet longer. A creamy suspension of the powder is made with about an equal quantity of fluid. This is applied to the wound surface with an aseptic syringe and then a thin layer of cotton soaked in the suspension is overlaid. This is levelled off with cotton wet with water and a flat layer of wet cotton placed on top. Several layers of vaseline gauze or fine meshed gauze impregnated with zinc oxide ointment complete the dressing. It should be changed daily but may go 2 to 3 days if conditions require infrequent dressings. The dressing comes off easily and does not stick to the wound. The old material is washed off with saline irrigation and the new dressing applied as before.

Adequate systemic administration of bacteriophage is any quantity

which does not produce a reaction but does have a favorable effect in reducing temperature and clearing the blood culture. When smaller doses do not suffice, I sometimes use as much as 150 cc a day. I cannot too strongly emphasize the fact that adequate tests must be performed to demonstrate the "double potency" of the phage against the infecting organism. To fulfill this requirement it must not only lyse the culture in fluid medium but show no growth when the lysed culture is transferred to a blood agar plate. Only if such potent phages are used will the mortality in staphylococcus septicemia be brought down materially by the use of bacteriophage.

Adequate systemic administration of the sulfonamide group of drugs is measured by the response to treatment on the one hand and the blood level determination on the other. These do not necessarily run parallel, but daily or every other day determinations should be done and the level maintained between 5 and 10 mg per cent. This is accomplished fairly regularly with sulfanilamide by giving an initial dose of 0.1 gm per kilo of body weight followed by 1 gm every 4 hours. The dosage of sulfapyridine and sulfathiazole are much more variable because of marked variations in absorption and elimination rates. Blood levels are correspondingly unstable. This fact plus the danger of urinary blockage from the acetylated compounds of these drugs makes them less satisfactory than sulfanilamide except in pneumococcus infections.

SUMMARY

In closing I would summarize this presentation by saying. In handling clean operative wounds all sources of contamination must be reduced to a minimum. In handling clean-contaminated operative wounds the kind of contamination can be predicted by the site of the operation and can usually be adequately met by appropriate measures. In handling accidental wounds a complete bacteriological analysis of the debrided tissue must be made by anaerobic as well as aerobic methods and specific treatment must be directed toward the organisms which are found to be present.

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VIRUS INFECTIONS*

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At the present time when one speaks of an infectious disease one usually thinks, because of habit, that such a disease is caused by a microorganism. As a rule, one does not stop to analyze just what one considers a microorganism to be, nor does one usually pause very long for thought about whether an infectious disease might be caused by an agent not classified as a microorganism.

For many centuries contagious diseases have been recognized, and infection was long an obvious fact before the cause of contagion or infection was known or understood. Then came the discovery of bacteria and protozoa, still considerable work had to be done over a period of many years with these tiny animals and plants before it was realized that they had anything to do with contagion and infection. The flowering of such an idea ushered in the microbiological era in infectious disease when it was firmly established that these maladies are caused by bacteria, fungi, spirochetes and protozoa. Indeed, it became so firmly established that these microorganisms produce infectious diseases that it was a heresy to consider them possible of causation in any other manner.

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Long before the microbiological era in infectious diseases, a method of preventing one infectious malady had been devised and its usefulness thoroughly established. I am speaking of vaccination against smallpox. When it was shown that microorganisms cause disease, investigators attempted to find a bacterium or a protozoan parasite responsible for smallpox. In fact, many different kinds of microorganisms were described as the etiological agent of this malady, but no agreement was reached regarding any of them. In 1898, the filterable virus era was vigorously initiated by the discovery that tobacco mosaic is produced by an agent capable of passing through earthenware filters, impervious to ordinary bacteria. Shortly following this, numerous agents, including those of smallpox and vaccinia, were shown to pass such filters and to be so small that it was impossible to see them by means of ordinary microscopes.

Thus, there came into existence, in addition to bacteria, protozoa, fungi and spirochetes, a group of agents now known and spoken of as viruses. As soon as this group was recognized, there immediately arose lengthy discussions regarding the nature of its members and the character of diseases produced by them. These discussions are still in progress, but fortunately much of the mystery and misunderstanding about viruses is gradually being dissipated. Perhaps some of the mystery is due to the fact that the agents producing virus diseases are not visible. For unknown reasons, it seems difficult for certain students of infectious diseases to accept the idea that some of the most powerful agents in nature do not possess a size compatible with visibility, and they still believe that the cause of an infectious disease must remain unknown, unidentifiable and mysterious as long as it is invisible. Until such an attitude has been relinquished, it will be difficult for anyone to clear away the mystery surrounding viruses and virus diseases.

There is no mystery regarding the importance of virus maladies, because they have always been, and still are, very potent factors in the economy and physical well-being of all forms of life. Indeed, from the highest form of life, man, to one of the lowest, bacteria, each stratum is involved. For instance, millions of dollars are lost each year because of virus diseases of plants and lower animals. Virus diseases of tobacco, potatoes, corn, tomatoes, beets, lettuce and sugarcane make great inroads upon our sources of income. Foot-and-mouth disease of cattle, hog cholera, swine influenza, cattle plague, fowl pox, equine encephalomye-

litis, swine pox, infectious tracheitis of chickens and avian encephalitis are also costly maladies. Man is subject to smallpox, yellow fever, measles, chickenpox, poliomyelitis and several kinds of encephalitis. Even the lowly bacterium, without which life of all forms on this world would quickly become extinct and our planet would be within a short time as barren as the moon, is subject to its own virus disease, bacteriophage. Even a casual survey of the diseases just mentioned is sufficient to impress upon anyone the reality of their importance and remove the notion that when an investigator talks about virus diseases he is dealing with something intangible and very mysterious.

The fact that there are infectious agents smaller than ordinary bacteria was discovered more or less accidentally through the use of filters specially designed to hold back bacteria while permitting the passage of their metabolic products, *e g*, toxins. The fact that these agents pass such filters led to their designation as filterable viruses. Filters can be made of all grades of porosity, in other words, there are filters with pores that permit the passage of bacteria, while others possess pores so small that ordinary proteins, as well as the viruses, are retained. It just happened that filters had been made to retain ordinary bacteria in order to separate their toxins from them. When such filters were used in certain kinds of investigative work, it was found that some infectious agents, capable of multiplication and for that reason not toxins, would pass through them. If other kinds of filters, that is very tight ones or ones with very small pores, had been used, the discovery of filterable viruses would have been delayed. Thus, the term *filterable virus* is somewhat misleading, because some viruses are difficult to filter, while a few very small bacteria are capable of penetrating certain of the more porous candles used in bacteriological work. At present most workers speak of viruses instead of filterable viruses because of confusion caused by the word *filterable*.

The fact that most viruses go through filters which retain ordinary bacteria is evidence that they are smaller than such bacteria. How much smaller was not known for a long time. However, very soon it was realized that all viruses are not of the same order of magnitude because certain of them pass filters that hold back others. Now we know the approximate size of a large number of viruses and the diameters of these virus particles range from 250 m μ to 8 m μ . Some viruses, for instance those of psittacosis and vaccinia are on the border of visibility by means

of ordinary microscopes, while others, namely, those of poliomyelitis and foot-and-mouth disease, because of their small size, will never be resolved by means of ordinary light. The fact that viruses pass filters impervious to ordinary bacteria and are invisible by means of ordinary light in the unstained state, should not immediately lead one to believe that all viruses are alike in nature or that all of them are necessarily quite different from minute bacteria. Indeed, certain very minute bacteria, which are capable of cultivation on ordinary lifeless laboratory media, pass filters as readily as do the viruses of vaccinia and psittacosis. Insofar as size is concerned, there is no reason to believe that these bacteria are much more complex than are the viruses mentioned. On the other hand, when one considers the viruses of poliomyelitis and foot-and-mouth disease, it is very difficult to imagine that they are as complex as bacteria, because they possess diameters of approximately 8μ which are only slightly greater than those of certain protein molecules.

Until proper means of concentration and purification of viruses were devised, one was left with conjectures regarding the complexity of their components. Within the last ten years great strides have been made, and during that time a number of plant viruses and a few of the animal viruses have been concentrated and purified to such an extent that one is warranted in drawing certain conclusions from their chemical analyses. In addition, some of the plant viruses have been crystallized and have been shown to be large molecules of nucleoprotein containing yeast nucleic acid. When this discovery was made in 1935 by Stanley, many investigators immediately concluded that all viruses probably would finally be shown to be molecular entities, either small or large, somewhat similar to plant viruses. However, workers who have been studying the nature of vaccine virus, the infective unit of which is spoken of as an elementary body, have come to the conclusion that this particular virus is much more complex than that of tobacco mosaic, inasmuch as it is composed of several different kinds of protein, including a nucleoprotein with thymonucleic acid, neutral fats, phospholipids, and other substances as yet unidentified. In other words, some investigators are inclined to look upon the elementary bodies of vaccinia as structures possessing qualities unlike those associated with ordinary molecules.

The complexity of vaccine virus is discernible not only by chemical examination but also through immunological studies. In fact, it is at times easier to differentiate between two proteins by means of immu-

nological techniques than it is by those of chemistry. From the investigations of a number of workers, it has been definitely shown that there are several antigens associated with vaccinal infections and that they in all probability derive from the virus. Thus, it appears that there are at least two soluble antigens, one heat-stable, the other heat-labile, which occur separately or as a complex. In addition to these, there are at least two others which are intimately associated with the elementary bodies or virus, e.g., an agglutinin and a substance that gives rise to neutralizing antibodies following an infection with the virus. A similar antigenic complexity has also been found in the viruses of infectious myxomatosis and psittacosis. In the case of these two diseases, however, antigens associated with the etiological agents have not been so thoroughly investigated as they have in vaccinia. The findings mentioned are quite different from those resulting from immunological investigations of simple viruses, e.g., that of tobacco mosaic which, so far as can be ascertained, is constituted of a single antigenic substance.

Most protozoa are easily visible and some of them are cultivable on artificial media containing no living cells. This is also true of the spirochetes. Fungi and bacteria are visible, and most of them have been cultivated on lifeless media. On the other hand, viruses, in addition to being invisible, are also uncultivable on lifeless artificial media, and, for that reason, many investigators concluded that there must be something mysterious about them and that of necessity they had to be different from ordinary microorganisms. Such a conclusion does not naturally follow, because there are bacteria which have not as yet been cultivated or induced to multiply outside of a susceptible host. The bacillus which causes leprosy is an excellent example.

It is true that no virus has as yet been induced to multiply in the absence of living host cells, but such a fact should not cast a veil of mystery over the virus group, because obligate parasitism is not an unknown phenomenon even among visible infectious agents, e.g., malarial organisms which multiply in a living host and not on lifeless artificial media. If some large infectious agents are obligate parasites, there is all the more reason for minute ones to require the assistance of host cells in carrying on the functions of life and multiplication. Indeed, beyond a certain point the smaller and less complex an infectious agent the more likely it is to be an obligate parasite, because of minute size it would not be capable of possessing all the necessary con-

stituents for autonomous existence. This matter has been discussed at length by Green who believes that all viruses are obligate parasites, even those of molecular dimensions. Obligate parasitism implies life, and Green believes that the nucleoprotein molecules of tobacco mosaic virus are living. According to him, multiplication is the only activity of which such a molecule is capable, the remaining activities necessary for such a living entity are carried out by host cells.

I admit that Green's ideas are plausible, but whether his scheme accounts for everything in the virus field is still a problem. At least there are other workers who think that some viruses, if not all, are manufactured by their host cells. According to them, there are substances in host cells which are precursors of viruses and which are converted into the virus agents through the action of proper stimuli, at the moment the only effective stimulus that is definitely recognized is some of the virus which is to be fabricated. There are excellent examples in the enzyme field to warrant such ideas, for instance, trypsinogen *in vitro* is converted into trypsin by the presence of a small amount of trypsin. At the present time Krueger and Northrop are carrying on extensive investigations with bacteriophage in attempts to show that this agent has precursors which are transformed into the virus under certain conditions. Unfortunately, as yet the results of their work are inconclusive.

From what has been said it appears that viruses are smaller than ordinary bacteria, some being much smaller, even approximating protein molecules in size, and that they do not multiply outside of a susceptible host. Furthermore, the indications are that the multiplication occurs within the involved or affected cell regardless of whether it takes place in a manner compatible with ideas regarding obligate parasitism or by fabrication through the activities of the host, aided by the processes of autocatalysis. This means that there is a very close relationship between viruses and their host cells. This close relationship between the infectious agent and the host cell undoubtedly accounts for many of the characteristic features of virus diseases. However, one must not forget that, inasmuch as there are intracellular parasites other than viruses, such features are not necessarily limited to virus diseases. On the other hand, no group of infectious agents as a whole exerts all of its forces through intracellular activity, and in that respect the virus group is unique.

As a result of the close relationship between viruses and their host cells, one of three things or a combination of these three things may occur. Rapid growth of a virus may cause immediate death of infected cells, or multiplication of the virus may first stimulate the cells and then destroy them, or, finally, the virus may act in such a manner that only stimulation of cells takes place. As one examines pathological tissues from virus diseases one sees that the things just mentioned have happened. In yellow fever, Rift Valley fever and foot-and-mouth disease the rapid growth and explosive action of the viruses lead to a picture of necrosis. In smallpox, fowl pox, vaccinia, chickenpox, and certain other virus diseases one sees early in the development of lesions only stimulation of infected cells which accounts for the formation of papules, later the stimulated cells making up the papular eruptions undergo destruction producing pustules or vesicles. Finally, in such conditions as Rous' sarcoma of chickens, Shope's papilloma, and warts, stimulation of cells is a prominent, if not the only, feature of the pathological picture.

Inasmuch as multiplication of viruses takes place within cells, it is not surprising that the phenomena just mentioned occur. In addition to this, in certain virus diseases inclusion bodies, which may or may not be made up of virus elements, are seen in the nucleus, in the cytoplasm, or in the nucleus and cytoplasm of infected cells. These inclusions are not necessarily pathognomonic of virus diseases, because some have been described in the absence of demonstrable viruses. Yet, as a rule, typical inclusions put the initiate on the lookout for a virus and at times may indicate the type of virus to be searched for, for that reason they are a great aid to virus workers.

Most physicians have been taught that inflammation is a prominent feature of infectious diseases. Inflammation occurs in virus diseases, but it is not a primary phenomenon, it is secondary to cell destruction. Many infectious diseases caused by agents other than viruses are characterized by an outpouring of polymorphonuclear leukocytes. In virus diseases, however, the inflammatory reaction is usually characterized by mononuclear cells. There are exceptions to the rule in both instances, and as yet one cannot account for the rule or the exceptions.

From what has been said about the close relationship between the host cell and virus agent, one might expect that viruses would exhibit selective localization, they do. Some viruses attack only certain hosts

that is, they are quite host-specific. Not only are they host-specific, but frequently they attack only certain cells within these hosts. Indeed, a few investigators have attempted to classify viruses by the type of cell attacked, dividing them into epitheliotropic, neurotropic, endotheliotropic, mesotheliotropic, and pantropic agents. Such a classification, unless used very loosely, is not satisfactory, because, although there is a tendency for viruses to limit their activities to certain cells, only a few of them limit their attack to one kind of cell. Perhaps the best examples of the strict tropism of viruses are Shope's papilloma of rabbits which attacks only epidermal cells without involving the epithelial tissues of the buccal mucosa, and the wart virus of Kidd and Parsons which produces lesions in the epithelial cells of the buccal mucosa of a rabbit but not in those of the skin.

One must not entertain the idea that selective localization of infectious agents is limited to virus diseases, because a similar phenomenon is observed in other types of infection. It is well known that the meningococcus is likely to involve the coverings of the brain and cord, that the pneumococcus usually causes pneumonia, and that the typhoid bacillus generally produces an enteric infection. All the reasons for the selective localization of infectious agents, whatever their nature may be, are certainly far from being known.

Although viruses often attack more than one kind of cell, the clinical pictures produced by them for unknown reasons are usually consistent, thus enabling clinicians to make proper diagnoses with a fair amount of regularity. For instance, in spite of the fact that the viruses of measles, varicella and smallpox enter the susceptible hosts by way of the same portal and are distributed throughout the body by means of the blood, clinicians are usually able to distinguish between these three maladies. In view of the fact that viruses and other infectious agents exhibit selective localization and since some virus diseases can be diagnosed from clinical pictures alone, one must not immediately conclude that all virus diseases can be diagnosed without the aid of laboratory techniques. This is particularly true of infectious diseases of the central nervous system. In other words, one cannot forthwith differentiate between the pyogenic infections of the meninges without laboratory aid, nor can one on clinical and pathological grounds alone with any regularity correctly diagnose virus diseases of the central nervous system.

If it is difficult to differentiate one virus disease from another by

means of clinical observations alone, or if one encounters trouble distinguishing virus diseases from maladies caused by other kinds of infectious agents, how can these things be accomplished with precision? There is nothing mysterious about the matter, one goes about diagnosing virus diseases just as one proceeds in arriving at a proper diagnosis of other infectious maladies. The general principles are the same, the differences lie in the techniques used. In the first place, one attempts to isolate and identify the virus responsible for the trouble. Frequently this is possible, as in the case of psittacosis, yellow fever, rabies and influenza. At this point in the procedure the only difference between virus diseases and other infectious maladies is that one does not use ordinary lifeless media to cultivate and isolate a virus. Instead one employs living media, e.g., small laboratory animals, developing chick embryos, or modified tissue cultures.

Many of the viruses act in a characteristic way in the living media and from this an experienced laboratory investigator obtains a clue as to the nature of the virus with which he is working. This is not unlike what the bacteriologist does when he makes cultures of microorganisms on agar plates or in broth, from the appearance of the colonies and by means of proper stains, etc., clues are gotten regarding what organism is being handled. From the appearance alone of a bacterium or from what a virus does in its living medium, one cannot be certain as to the identity of the infectious agent. In both instances it is necessary to proceed further through the use of different kinds of media, e.g., in the case of bacteria, media containing various sorts of sugar for fermentation tests, and in the case of viruses, different laboratory hosts for the establishment of the host range. Having done this, the worker has further information regarding the identity of the virus, still he may be unable definitely to classify the organism or the virus. At this point he turns for aid to classical immunological reactions. These are the same regardless of the type of infection being studied, agglutinations, precipitation reactions, complement-fixing reactions and neutralization or protective tests are used.

Immunological principles are broad and are universally applicable provided one understands them and is ingenious enough to devise ways of applying them. Probably the first immunological phenomenon to be noted was in connection with virus diseases. Many centuries ago it was observed that individuals recovering from certain infectious mal-

dies, e g, smallpox and measles, usually possessed a lifelong immunity. Such an enduring immunity is most striking in virus diseases, although it is known to occur in other infections. In the study of virus diseases use is made of this phenomenon in the identification of their etiological agents. Animals are infected with known viruses and after recovery they are inoculated with the unknown agent. If among the viruses used for the original inoculation there is an agent similar to the unknown, then the animal receiving that particular agent would be resistant to the unknown and in this way indicate the identity of the unknown. Such a procedure is not unique for virus studies, because it is used also for the identification of other kinds of infectious agents or their toxins.

During the last 100 years antibodies were recognized and came into use for the identification of infectious agents and for the diagnosis of infectious maladies. About forty years ago it was shown in regard to virus diseases, e g, in the case of smallpox and vaccinia, that serum from a convalescent animal mixed with the virus responsible for the malady protects a susceptible or non-immune animal against the virus in the mixture. This procedure is known as the neutralization or protection test, and is used extensively in the identification of viruses and for the diagnosis of virus maladies. This test is not unique, because it is similar to those used for the identification of toxins, bacteria and the diseases caused by them.

The complement-fixation test was the next immunological reaction to be used in the study of viruses. Jobling, in 1906, showed that serum from an animal convalescent from a vaccinal infection upon being mixed with vaccine virus would specifically fix complement. In 1913, Paschen demonstrated that elementary bodies of vaccinia and smallpox were specifically agglutinated by serum from individuals convalescing from these infections. Then came the work of Craigie and others showing that in the case of certain virus diseases there are soluble antigens separable from the viruses themselves which precipitate in the presence of specific immune sera. These soluble antigens also fix complement under proper conditions. Thus, it is obvious that the immunological tests used in the study of virus diseases are in principle exactly like the ones employed in other infectious fields. All that is required is that one banish ideas of mystery and set oneself to the task of learning the details essential for success.

Now in regard to the treatment of virus diseases. Is there anything

peculiar about this aspect of the virus problem and is it different from those associated with other kinds of infectious diseases? With a few possible exceptions, one can immediately say, no. In spite of a few antibacterial sera and antitoxins, the treatment of bacterial infections until recently was largely expectant. Chemotherapy in the last few years has changed the whole picture. As yet, however, no great advance in this direction has been made in the virus field. It is true that certain reports have appeared stating that lymphogranuloma inguinale and trachoma are benefited by some of the sulfonamide compounds. Despite the meager results so far obtained, there is no reason to suppose that great advances in the treatment of virus diseases will not be made in the future by means of chemotherapy, indeed, this seems to be the most likely source of curative agents for this type of malady.

At the moment, the treatment of virus diseases in general is still expectant. One might inquire why serotherapy has not been successful in virus maladies. It certainly is not for the lack of intensive effort. Most of the virus diseases have been treated by immune sera, but unfortunately the results have not been encouraging. As one considers the problem in the light of what is known about viruses, one is forced to the conclusion that serotherapy of the diseases caused by these agents is not likely to yield desired results. A reason for this is found in the fact that viruses are intracellularly situated. Since antibodies do not enter cells, such a situation makes it impossible for the antibodies in therapeutic sera to reach the infectious agents. Still, one might well ask why antibodies therapeutically administered do not attack viruses as they leave infected cells on their way to attack normal cells not already involved. They do because viruses in an extracellular location are susceptible to the action of immune sera. Then, why is it that immune sera are not efficacious in the treatment of virus diseases? A good deal of experimental evidence exists which indicates that in most virus diseases by the time signs and symptoms of infection are manifest, all of the cells that are going to be infected in that particular host have already been entered. In view of such evidence, one would not expect serotherapy to be of great value in the handling of these maladies. Undoubtedly there may be exceptions to the statement just made, but one should demand adequate proof of the therapeutic efficacy of all antiviral sera.

In the prevention of virus diseases there is at the present time little

to offer except quarantine measures, and several convalescent sera. Indeed, most of the quarantine measures seem fairly useless. I doubt very seriously whether measles, chickenpox, poliomyelitis, influenza and smallpox are influenced in the least by the quarantine measures now employed. Furthermore, I do not know of any that would be of use under our present social conditions. Except for making people believe that public health officials are doing something, it would seem to me that money spent on many quarantine measures might be used better in other ways. I trust there comes a time when lay people will be sufficiently informed and possessed of sufficient stamina to demand of public officials that expensive and unessential things which interfere with business and social activities be not done.

Vaccines originated in the virus field. The first successful vaccination was carried out by Jenner when he prevented smallpox by the inoculation of human beings with vaccine virus. This was accomplished on an empirical basis long before bacteria or similar agents were known to be associated with infectious diseases. Vaccination against smallpox is still the outstanding method of preventing a severe infectious malady. In spite of that, perhaps 40 per cent of the people in the United States are at this moment susceptible to smallpox. Vaccination against yellow fever has been perfected within recent years and bids fair to control outbreaks of this malady, provided public officials and the lay people are willing to see it properly used. A vaccine for equine encephalomyelitis has been developed, and perhaps in Horsfall's recent work with influenza and distemper there lies a method of preventing influenza. Tests of this influenzal vaccine are now under way, but it will be some time yet before an answer will have been obtained. There is every reason to suppose that eventually many more virus diseases will come under control through the use of properly prepared vaccines, and it is for this reason that investigators are willing to spend many tedious hours in carrying on work that frequently yields disappointing results.

How do viruses spread in nature? There is nothing peculiar or characteristic about the spread of viruses. Most plant viruses are spread by insect vectors. A few virus diseases of man are spread in this manner, e.g., yellow fever by the mosquito. Spread of the majority of virus diseases of man that we know about at the present time, however, seems to be accomplished through contact or by means of droplet infection. Of course this means that, unless one can sterilize and keep sterile the

air which one breathes daily, it will always be difficult to control virus maladies through sanitary measures alone

Undoubtedly some will ask why is there nothing peculiar about the epidemiology or spread of virus diseases in a population, since some of the agents causing these maladies may be fabrications of their host cells. Regardless of whether viruses are minute obligate parasites or whether they are inanimate fabrications of host cells, no virus disease has as yet been shown to arise *de novo*. Every case of a virus disease results from the entry of the virus into a host from another host. Thus, the spread of virus diseases, as is the case with other types of infectious disease, is wholly dependent upon transmission of the inciting agent from one host to another. Epidemics of virus diseases do not arise as a result of multitudinous, simultaneous foci of *de novo* fabrication of their etiological agents. A statement of this kind does not imply that new infectious agents have not come into existence during the past or that no new ones will develop in the future. Yet, so far as I know, there is no evidence to show that a single absolutely new infectious agent has come into existence during the time covered by the recorded history of man.

Upon viewing the matter dispassionately one finds that in many respects virus diseases resemble other infectious maladies. Furthermore, it is obvious that such diseases, including those displaying neoplastic phenomena, truly belong in the large category of infections. That they should be looked upon as something strikingly peculiar or even mysterious is due to a state of mind instead of factual evidence. Perhaps such a mental attitude can be accounted for to some extent by unfamiliarity with the subject.

It is true that viruses differ from other types of infectious agents, but that can be said of each of the other types. In spite of the facts that viruses are invisible, that they multiply only in living susceptible host cells, that all of them may not be alike in nature, and that some are crystalline proteins, the problems resulting from the invasion of a single host by a virus or from epidemics of virus diseases, and the general principles underlying methods of solving these problems are similar to those encountered in other infectious fields. From a practical standpoint it makes little difference at the present time whether a virus is an inanimate crystalline protein or a minute obligate parasite. In fact, the actions of bacteriologists, epidemiologists, immunologists, physicians and public health officers would not be affected immediately by final deci-

sions regarding the nature of all agents now classified as viruses. On the other hand, knowledge obtained in arriving at such decisions would be of inestimable value at some future time not only in regard to a better handling of virus diseases but also in regard to a better understanding of general biological phenomena. For that reason many virus investigators are willing to toil without thought of immediate reward in the hope of eventually making a worthwhile discovery.

POLIOMYELITIS*

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SEVERAL different aspects of the poliomyelitis problem will be considered in this paper first, the environment in which epidemic poliomyelitis seems to thrive, second, some clinical aspects of the disease, and third, theories which concern its mode of spread

ENVIRONMENT

The picture in Figure 1 is a reminder that poliomyelitis is a summer disease, which flourishes in a rural setting. Actually the scene illustrates the site of the first reported case in a recent Connecticut epidemic,¹ but the general setting may be familiar to anyone who has had occasion to see many cases of poliomyelitis. It might be reduplicated over and over again during poliomyelitis epidemics in many States of the Union. There is, of course, no doubt that poliomyelitis epidemics are common enough in cities, but it is the frequent severity of the epidemics in the country that concerns us. Something important causes this disease to flourish in the country during the summer. This may be entirely due to an increased susceptibility among rural children, but in recent epidemics the age distribution of both rural and urban cases has been such as to render this explanation unlikely. Whatever the rural factor or factors may be, they have not received as much emphasis in this country as we believe they deserve, for they must be almost as fundamental, from the standpoint of etiology, as is the virus itself. In any event the recognition of the existence of these factors has led us to regard a local epidemic of poliomyelitis as an indication that the "place is infected," as well as some of the people in it. In other words we do not believe that poliomyelitis is a contact disease per se, but that the proper environmental setting is more important for the spread of the disease than is the mere presence of the virus among a group of susceptible children.

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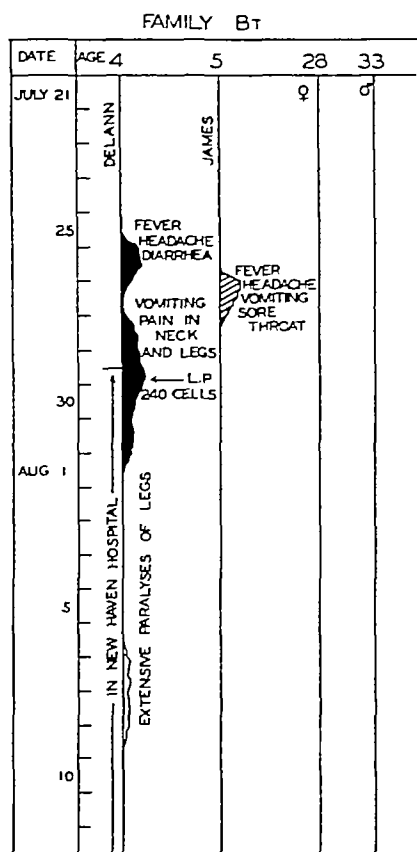


Fig 1—A picture of the rural surroundings in which epidemic poliomyelitis flourishes. The scene is taken from an actual epidemic. Some of the children shown here are convalescent from abortive attacks and are intestinal carriers of the virus. Note the open sewer emptying into the brook. Insert outline map of the State of Connecticut.

CLINICAL CONSIDERATIONS

Clinical poliomyelitis may assume several forms but by far the commonest, is abortive poliomyelitis. It is also the most difficult to diagnose. There are no inexpensive diagnostic tests and no distinctive clinical features whereby abortive, or suspected abortive cases of poliomyelitis may be recognized, and so the clinician must fall back on his clinical judgment, which must be brought to bear not only on the patient but also on the circumstances under which these illnesses appear. For instance, when two children in the same family fall ill during a poliomyelitis epidemic with about the same symptoms, and after a day or two one child emerges from the illness with a paralyzed limb, whereas the other does not, it is fair to suspect that the milder illness of the two also may have been poliomyelitis (Fig 2). And, as a matter of fact, it is occasionally possible to substantiate the diagnosis of abortive poliomyelitis by laboratory determinations, if one is fortunate enough to be in touch with a laboratory that can perform these time-consuming, difficult, and expensive tests. Perhaps it may seem like a waste of time to be placing emphasis on the mild form of the disease, but without an appreciation of the

Fig 2—Diagram of a fairly typical family with poliomyelitis. Vertical lines indicate the family members, their ages appear at the top. Both children became ill at about the same time, eventually one became paralyzed. The presence of paralysis aids in the clinical diagnosis but it does not aid in determining which of the two children will excrete the most virus in their stools.



concept of abortive poliomyelitis it is harder to grasp the real significance of this disease. The parents of a family of children can perhaps afford to be interested only in paralysis, but not so the physician. His best chance of discovering the true incidence of infection is to observe the abortive as well as the paralyzed cases. As abortive cases outnumber the paralyzed cases by 4 to 6 times in some epidemics,² they can also be a tremendous source of virus in the community. It may be recalled, for instance, that both types of poliomyelitis cases may harbor large amounts of virus in their stools particularly during the first three weeks of convalescence. But the abortive cases may scatter the virus more widely, for unlike the paralyzed case which is confined to bed, either at home or in the hospital during this period, they are allowed to roam about it will as soon as their brief period of fever is over (Fig 3).

Symptomatically the mild abortive case is characterized as a brief illness usually with fever lasting from a few hours to a few days which

ABORTIVE CASES OF POLIOMYELITIS ARE MILD AND ACT AS HEALTHY CARRIERS

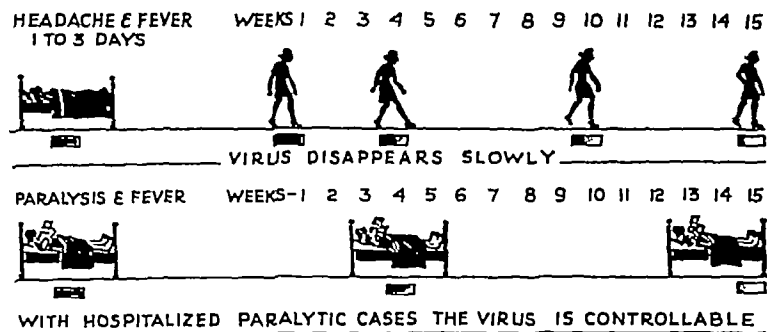


Fig 3—The ambulatory patient convalescent from an abortive attack can act as a widespread source of virus in the community

is accompanied by one or more of the following symptoms fever, headache, vomiting, lassitude, occasionally sore throat, and occasionally diarrhea, often a little pain in the back and occasionally a stiff neck. When I speak of fever I mean a temperature of 101° or more, which is unexplained on any other basis, and when I refer to pain in the back, it is well to recall the spine sign as the most valuable method for its detection. The lumbar puncture nearly always yields negative results in these cases. These diagnostic aids sound vague, but in spite of the non-specific character of this illness the diagnosis of abortive poliomyelitis is made with more confidence and more often today than it was ten years ago. The practical lesson is that, during a poliomyelitis epidemic, all children who suffer from a nondescript febrile illness should be put to bed for a longer period of time than is done under other circumstances. This should be done cautiously, and with every effort to allay a hysterical response on the part of the parents of the patient, but actually such patients should be treated with almost the same solicitude as the paralyzed ones, for how can one tell when an abortive case is going to turn into a paralytic case. This brings us quickly to a consideration of the treatment of choice during the so-called preparalytic phase.

I hesitate to recommend any definite therapeutic course but will merely describe what we do, at present, and why we do it. In principle we follow the same measures that are employed in the early stages

of any brief febrile infection, but in this disease we try to guard the patient carefully, and to protect him from all forms of *meddlesome therapy*. We are apt to prolong the period of bed rest beyond that which is ordinarily employed [If the patient does develop paralysis, the physician's task, of course, is to assist in allaying irritability, to protect weak or paralyzed limbs, and to support any impaired functions of the body, such as difficulty in voiding, in swallowing, or in breathing. After the active stage of paralysis is over, the management of poliomyelitis patients becomes largely a problem in orthopedics.] But the reason we do so little in the early stage is to avoid the possibility of harmful procedures. Clinical judgment (and we have no statistics to prove this) indicates that trauma of almost any kind may often turn a case in the wrong direction. Among traumatic procedures, I would include unnecessary vena punctures or lumbar punctures, the administration of strong purgatives, the injection of foreign protein, and (with reservation) even the injection of human serum. The point is, that when a child's fate is hanging in the balance as to whether the virus is going to damage the central nervous system severely or not, it seems better to do nothing rather than to do something which may not only be of unproven value, but also may fall under the category of a traumatic procedure. In support of this thesis, the best series of cases on record, that is the series with the lowest mortality and the lowest incidence of paralysis, received nothing but bed rest.³

As for the question of serum therapy we could easily devote our full period of time to a discussion of the pros and cons of this subject but I will dispatch this difficult question with the brief statement that at the New Haven Hospital we do not use serum at present, I do not wish to imply that it should never be used.

So much for therapy, next, what are the physician's duties with regard to prophylaxis? This is a subject which most authors would like to avoid, in any event, it is well to appreciate that the procedures are certainly subject to change from year to year. We believe that when poliomyelitis appears in a community it is wise to seek the immediate advice of the local health officer so that a uniform plan may be adopted in which all local physicians may join. The usual questions to be decided are: What should the attitude be with regard to the abortive case? Should the stools of all patients be disinfected as in typhoid fever? Should the schools be opened or closed? Should one advise that all

drinking water be boiled? Should one advise people to leave town? Should one advise the use of "antiserum" as a prophylactic measure? The answers to these questions are difficult indeed and they depend on the local situation, but there are two recommendations perhaps which are not local. First, it seems reasonable to discourage swimming in epidemic areas where the water has a possibility of being contaminated with local sewage. In justification of this recommendation I may say that there is little or no proof that poliomyelitis has ever been actually contracted from swimming, but there is proof that during epidemics, virus has been detected in sewage.^{1,4} The thought of allowing children to bathe in virus polluted waters is, at least, unpleasant. Second, a ban should be put on all tonsillectomy operations during the epidemic period—A tonsillectomized child may fall into the category of a "traumatized" child, evidence points to the fact that the disease is more severe in a child whose tonsils have been removed within a year than in control children.⁵

MODES OF SPREAD

Next as to current theories about the portal of entry of poliomyelitis virus in man. This is a controversial question and the best that we can do is to mention a few of the theories. For at least 20 years the belief has been widely held in this country and elsewhere, that poliomyelitis was a contact disease, spread perhaps by droplet infection, that poliomyelitic virus penetrated the nasal mucosa and entered the human body through the olfactory bulbs. One may recall that this theory gained popularity because it had been found experimentally that poliomyelitis could be produced by instilling the virus into the nose of the monkey. However, years later it was discovered that this technique was effective in other diseases too. For instance, it is now recognized that mice can be infected by the nasal instillation of yellow fever virus and rabies virus. Yet neither of these experimental procedures with mice tells us about the manner in which man acquires yellow fever or rabies. And so the original interpretation of the nasal experiments with poliomyelitic virus in the monkey begins to lose some of its force. One cannot deny that the nasal theory is possible, but we recognize today that there may be a number of ways whereby the virus may enter the body and, of these, the nasal route seems to be the most unlikely in man. The main evidence on which this last statement is based comes from the work of Sabin and Olitsky,⁶ and

TESTS FOR POLIOMYELITIC VIRUS IN NASOPHARYNGEAL WASHINGS AND IN STOOLS IN VARIOUS WEEKS OF POLIOMYELITIS

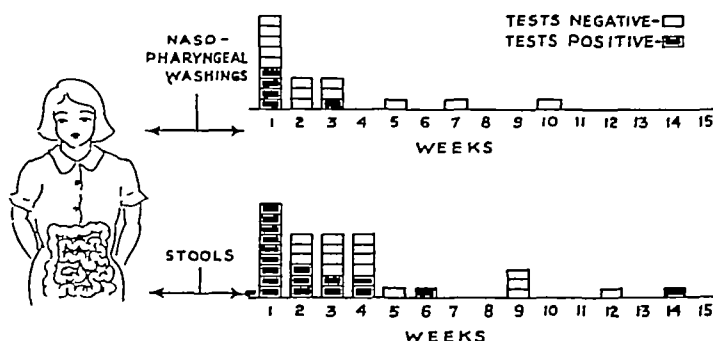


Fig 4—The virus can be detected in the stool more readily than in the nasopharynx, and it persists for longer periods there.

others who report that human autopsies have so far failed, almost universally, to reveal those lesions in the olfactory bulbs which occur with such regularity when the disease is produced experimentally in the monkey by instilling the virus into the nose. The increasing number of negative olfactory bulb findings in human autopsies therefore indicates that portals of entry other than the nasopharynx exist in the human disease, although the nasopharynx has not been eliminated. As a matter of fact, poliomyelitis actually can be produced in man (as in the monkey) by an “extranasal” route, namely, by injecting virus under the skin. This was done accidentally, of course, when vaccines were being tried as a prophylactic measure in this disease some years ago.⁷

The next question which naturally follows a discussion of the portal of entry concerns the portal of exit of the virus. As you know poliomyelitis virus has been recovered from both the nasopharynx and the intestinal tract during acute and convalescent stages of the clinical disease. It is easier to recover virus from the intestinal tract than from the nasopharynx, and in both paralytic and abortive cases it persists there for longer periods of time, as shown in Figure 4, and, thanks to a new and simplified technique of Howe and Bodian¹⁰ the stool is now becoming a diagnostic measure in this disease. Regardless, then, as to where the portal of

* Howe and Bodian found that the introduction of small quantities of stool suspension into the nose of monkeys could induce experimental poliomyelitis in 10 out of 14 cases.

entry of the virus is, an important portal of exit is the anus. Furthermore, as poliomyelitis virus is also very resistant (for one may recall that it withstands 1 per cent phenol, or 15 per cent ether), it is not remarkable that under certain circumstances this virus should appear in sewage. Other pathogenic agents may also be found in sewage, notably tubercle bacilli, and so the mere presence of poliomyelitic virus in this medium tells us nothing about the way this disease is spread, but it is interesting to know that it is there, and that it may be there in such large amounts, for one determination made during the 1939 epidemic in Charleston, South Carolina indicated that more than 18,000 doses infective for the monkey, were passing through one particular sewer each minute of the hour on which the test specimen was taken.

To summarize our views on the unsettled question of the modes of spread we believe then, that the nasopharyngeal portal of entry in the human disease is unusual, and we believe, as do others, that poliomyelitis is probably transmitted from one person to another through a number of different channels. Among these, may be that of close and intimate contact, but the situation is certainly not so simple as to be explainable on the basis of direct contact alone. Furthermore, it would seem unlikely that poliomyelitis is a true water-borne disease, for again the situation is not so simple. Whatever the real epidemiological situation may be, it is likely to be a complex conditioned largely by summer weather and aided by rural environment. One may recall in this connection that the presence of virus in sewage or water allows it to come in contact, particularly during the summer, with an immense number of living things. It again raises the question as to whether there may not be an extra-human host or hosts in this disease, in which insects, mammals or birds may play a part. As yet there is no real evidence for this, but the circumstantial evidence for an extra-human reservoir of virus in this disease is at least good.

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EPIDEMIC INFLUENZA *

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I N 1933, Smith, Andrewes and Laidlaw¹ announced that they had isolated from the nasal washings of influenza patients a virus which was pathogenic for ferrets by the intranasal route. The following year this observation was confirmed in our laboratory where strains of the same virus were recovered from epidemics in Puerto Rico,² the United States³ and Alaska.⁴ At the same time it was found that mice were also susceptible to the virus infection when anesthetized and inoculated intranasally.^{2,5} Since then, the virus has been clearly established as the causative agent of epidemic influenza by the application of experimental methods to the study of individual cases in different epidemics.

THE DIAGNOSIS OF EPIDEMIC INFLUENZA

The laboratory diagnosis of epidemic influenza has employed essentially two approaches. The first, consisting of the isolation and identification of virus from the patient, is perhaps the most conclusive but also the most tedious and expensive. Commonly, the nasal washings of the patient are passed to ferrets and subsequent transfer of the virus is made to mice, where it can be satisfactorily identified by serological means. One can, however, allow the inoculated ferret to recover. In this case the presence of virus in throat washings is demonstrated by the appearance of antibodies to the virus in the animal's serum or in its capacity subsequently to resist active infection with known virus. Either method yields valid evidence of the presence of virus when positive, negative results are somewhat less significant.

The second approach makes use of the fact first demonstrated by Francis and Magill³ that infection of human individuals by the virus of epidemic influenza calls forth a sharp rise of antibodies in the convalescent serum. While it is known that antibodies are detectable in a large proportion of normal sera, by comparing serum taken from the patient

* Delivered October 17, 1940, in the Graduate Fortnight of The New York Academy of Medicine

during the acute phase of illness with that taken after recovery, the increase in titer can be measured. Two techniques are available: (1) the determination of the smallest amount of serum capable of protecting mice against fatal infection with a constant amount of virus, thus measuring the titer of neutralizing antibodies, (2) the determination of the smallest amount of serum which fixes complement in the presence of a constant amount of virus antigen prepared from infected mouse lungs or tissue culture medium.

Efforts have been made to gain knowledge not only concerning the frequency of virus infection in typical cases but to study the marginal cases as well, hoping in this manner to map the boundaries of the clinical picture. These observations have also served, reciprocally, to establish the value of the laboratory procedures for practical clinical purposes.

In order to demonstrate the frequency with which influenza virus can be identified in epidemic influenza patients, it will be well to summarize the experiences of various investigators in the winters of 1936-37 and 1938-39. Together with Magill, Rickard and Beck,⁶ at the laboratories of the International Health Division, during the epidemic period from December 1936 to March 1937, material for study was obtained from 100 patients in whom a final diagnosis of epidemic influenza was made. Throat washings from 64 of them were tested by ferret inoculation and in 52, or 81 per cent, the presence of virus was demonstrated. From 23 of the washings, strains of virus were actually established in mice. In England, Stuart-Harris, Andrewes and Smith⁷ similarly reported 75 per cent successful tests for virus from 40 typical cases although the number of strains transferred to mice was low. Moreover, in numerous other laboratories throughout the United States, Europe and the Far East, additional strains of the virus were recovered. Thus, from an epidemic of moderately severe influenza, pandemic in its distribution, the presence of the virus was demonstrable with relative ease in a high proportion of the patients attacked.

The results of 1938-39 offer an interesting contrast. The disease was not prominent in the general population but appeared more in the form of institutional outbreaks. Moreover, the clinical attacks were quite mild. Stuart-Harris, Smith and Andrewes⁸ reported the recognition of influenza virus in only 7 of 59 throat washings obtained in 12 institutions. All of the positive results were had in late February or March. The strains of virus were of low pathogenicity for ferrets and were

adapted to mice with difficulty Horsfall, Hahn and Rickard⁹ studied 4 localized epidemics in January to March 1939 Throat washings from 65 cases were subjected to repeated ferret passage Of these, 14 gave rise to antibodies in the ferret and 9 strains were adapted to mice Our investigations in the same period apply more to the general population No epidemic was recognizable Throat washings were obtained from 28 selected patients among the nursing staff and patients on the wards of the Third Medical Division of Bellevue Hospital In 3 instances the presence of influenza virus was shown by the development of antibodies in the inoculated ferret¹⁰ No strains were established in mice In Australia, Burnet and Lush¹¹ reported the isolation of mild strains of virus in July 1939

Hence, in the early months of 1939 when mild isolated outbreaks were observed in different parts of the world the virus was less readily isolated and the incidence of detection was approximately one-third that noted in the more severe outbreak of 1936-37 The uniformity with which virus can be recovered appears, therefore, to be related to the pathogenicity of the prevalent strains of virus and it becomes obvious that this procedure is unsuited to the diagnosis of a large number of individual cases

Serological studies were also carried out in relatively large numbers of patients Their value was established by a consideration of the results of the neutralization or complement fixation tests in relation to virus identification Thus, in 1937 titrations of neutralizing antibody were made with acute and convalescent sera of 41 patients from whose throats virus had been recovered⁶ In each instance a sharp rise in the titer of the convalescent serum was observed The average titer in the early days of illness was 22 while in convalescence it reached the high level of 235 The uniformity of response indicated that the virus infection and the increase in titer were associated phenomena When comparable antibody responses were observed in the sera of patients from whom either virus was not recovered or throat washings were not collected, it was reasonable to conclude that the rise of antibodies was due, nevertheless, to infection by the same virus Conversely, those cases of various clinical types, from whom virus could not be recovered and whose convalescent titer was essentially unchanged from the normal level were considered to have suffered from infections of different etiology The results of the neutralization tests were verified by Stuart-Harris, An-

drewes and Smith⁷ in a study of sera from 23 patients in the English epidemic of that year

Following a procedure similar to that described by Fairbrother and Hoyle¹² the same sera were then tested in the complement fixation reaction.⁶ Results, strikingly comparable with those of the neutralization tests, were obtained. An average rise in titer of tenfold to twentyfold was recorded in sera from the groups of patients which had yielded the positive neutralization tests. The groups of sera which yielded negative results by the neutralization test revealed no significant change in the complement fixation titers.

Hoyle and Fairbrother¹³ had also noted the rise in complement-fixing antibodies during convalescence in 8 patients and observed further that the titers of convalescent patients were, in general, considerably higher than those of the general population tested immediately prior to the epidemic.

In the mild epidemic of 1938-39, when the incidence of virus detection was low, the serological tests maintained their efficiency in identifying cases of the disease. Stuart-Harris, Smith and Andrewes⁸ were, by the neutralization test, able to demonstrate the occurrence of epidemic influenza in 4 institutions when virus was not isolated. At New York University virus¹⁰ was demonstrated in only 3 of 28 patients. Acute and convalescent sera were obtained from 14 of the patients, however, and half of them showed the characteristic rise in neutralizing antibodies. The extensive studies of Horsfall, Hahn and Rickard⁹ during the same period are extremely noteworthy. While in only 21 per cent of throat washings tested was the presence of virus proven, neutralization tests with the sera of these patients revealed a diagnostic increase of antibodies in 93 per cent. But, strikingly, in only one of 83 patients with non-influenzal respiratory infections was a comparable mounting of the titer observed. This shows clearly the significance of the test in establishing the etiology of the disease in a large group of patients which otherwise would not have been identified. The value of the serological reactions has thus been tested in two epidemics of greatly different severity and extent. One, with a high incidence of infection in the general population, pandemic in distribution, demonstrated the causal relationship of virus infection and positive serological tests, the other, recognized primarily in institutions in this country and abroad, was caused by virus which produced a mild illness and was of low pathogenicity.

for animals. In this outbreak the significance of the serological tests was enhanced, for, while virus was isolated from only a minority of cases, the circulating antibody titers identified the individual case just as accurately as in the preceding epidemic.

The investigations have confirmed the accepted theory that influenza is an epidemic disease in which a high proportion of cases presents a great uniformity of symptoms. It has been demonstrated, however, that distinct variations may occur. Thus, in 1936-37 in a group of contacts who exhibited no signs or symptoms of the disease, serological studies revealed that approximately 25 per cent had actually undergone virus infection. A similar incidence is recorded by Horsfall, Hahn and Rickard⁹ in 1939. The importance of clinically undetected cases as agents of dissemination becomes apparent.

Certain information has been gained concerning the so-called relapses which some authors have considered a characteristic of epidemic influenza. There is ample evidence that serious pulmonary disease may follow what appears to be simple influenza. The most common is a mild bronchitis or bronchiolitis which develops slowly as the acute illness subsides. The usual story of the relapse is, however, that about the time of recovery the patient has a recurrence of fever and may then develop pulmonary disease. Numerous observers have considered such episodes to be secondary infections and the evidence of the virus studies clearly supports this conclusion. In 1936-37 we had the opportunity of studying material from 7 such patients.⁶ They gave histories of moderate illness for 6 to 8 days and a sudden exacerbation of symptoms and fever prior to their admission to hospital. Bacteriological diagnoses of atypical pneumococcus pneumonia had been made in 2, acute pneumococcal bronchitis in 1, hemolytic streptococcal tracheitis in 1, 3 were simply called relapses of influenza. At the time they were first observed in the hospital, the serological tests revealed high antibody titers quite characteristic of the patient convalescent from virus infection. Virus was not detected in the 3 throat washings tested. It is evident, therefore, that the relapses were bacterial infections developing in convalescence from the virus disease. Stuart-Harris⁷ has recorded relapses due to pulmonary disease in 3 patients and in 5 others due to acute hemolytic streptococcal tonsillitis. Cases of this general character illustrate clearly the lack of reason in considering the relapse a recrudescence of the primary virus infection. They are obviously caused by secondary bacterial invaders.

The same comment applies to the post-influenzal pneumonias occurring within a short interval after recovery. On the other hand, the British group⁷ have reported the isolation of virus from 3 patients dying of pneumonia within 5 days of onset of influenza. In all of them cultures of the lungs revealed heavy growth of *Staphylococcus aureus* as well. We also⁸ recovered virus on the second day of the disease from a patient with a simultaneous bacterial infection due to *Pneumococcus* Type III. This indicates that the possibility of severe respiratory disease beginning synchronously with the onset of the virus infection is an attribute of the bacterial agent. It is noteworthy that through the epidemics discussed, bacteriological studies have not disclosed a preponderance of a particular organism. In fact, the great majority of cultures have resembled the normal nasopharyngeal flora. It seems likely that the differences in mortality in different epidemics depend upon the nature of the bacteria prevalent at the time and that any of the common respiratory pathogens may be responsible for the serious complications.

Recognition of the average cases in the course of an epidemic is aided by their relative uniformity. A sudden onset is the rule, with fever and constitutional symptoms in the absence of prominent respiratory complaints such as the sore throat of tonsillitis or the nasal discharge of the common cold. The course is short and convalescence is relatively prompt except for residual fatigue. Either leukopenia or the absence of leukocytosis in the early days is a significant observation. Nevertheless, a diagnosis of epidemic influenza in the individual patient, considered out of relation to an epidemic, can not be made purely on the basis of clinical observation. In fact, the readiness with which a diagnosis of influenza is made under these conditions is inversely proportionate to the physician's diagnostic accuracy. Because of this, the early cases of an epidemic in a general population are usually recognized in retrospect. Moreover, epidemics and outbreaks of diseases as remote as yellow fever and lymphocytic choriomeningitis have been so diagnosed. These facts illustrate the relative non-specificity of the symptom complex.

Just as the confirmation of clinical diagnosis in so many illnesses depends upon the use of laboratory aids, so is it in epidemic influenza. Only with increasing efforts to establish the diagnosis etiologically will the clinical problem be solved. One can point out certain differentials which should be made and maintained. Epidemic influenza applies to

the disease in its abrupt epidemic form, there is no evidence to date that sporadic cases of the virus disease occur except in relation to an epidemic period. It is essentially a febrile, prostrating, brief disease, it is not the afebrile common cold with profuse discharge but with few constitutional symptoms, nor is it the purulent complication of the common cold. In acute pharyngitis, tonsillitis or sinusitis caused by the hemolytic streptococcus, pneumococcus, staphylococcus or Pfeiffer's bacillus the organisms can be identified, if the effort is made, these are not epidemic influenza. While a certain number of patients with epidemic influenza may have gastrointestinal disturbances, as is the case with numerous acute infections, there is little justification for the term, intestinal flu, etiological investigations have usually revealed food or water borne infection in outbreaks so designated.

There is in addition that group of irregularly distributed, low-grade respiratory infections of the winter season which the British writers have called febrile catarrh.⁷ They bear little close resemblance to typical epidemic influenza but more probably represent bacterial infections of low pathogenicity and transmissibility. The use of the term, febrile catarrh, may well be a suitable one provided there is at the same time an admission that it is merely descriptive. No single etiology for these cases has been recognized.

Mention must also be made of certain epidemics bearing a close resemblance clinically and epidemiologically to those caused by the virus of epidemic influenza but in which all reported studies have failed to implicate that virus. One such epidemic was widespread throughout the entire United States early in 1936,⁴ another this year. These outbreaks have recently been shown to be caused by a new type of virus¹⁴ clearly different from that previously recognized. The entire field must, therefore, be reinvestigated in this light.

I have tried to show how the investigations to date have established the virus etiology of epidemic influenza and to summarize representative results from which that conclusion is drawn. Through the methods outlined a definitive picture of the disease and its variations is taking form. In this instance, as so often before, the establishment of diagnosis on the basis of etiology is serving to bring order in a field of infection which has been the source of marked clinical confusion.

To many minds the term, epidemic influenza, connotes only the devastating disease of the autumn of 1918. A survey of the history of

influenza reveals on the contrary that the world-wide scourge of 1918 looms from the pages of history as an episode without counterpart in the centuries through which physicians have recorded the characteristics of its not infrequent visitations. It was not unique in its spread throughout the world, it was not unique in the proportion of the population attacked or in the fact that it was looked upon as something entirely new to that generation of physicians. The rate of dissemination, the frequency of severe pneumonias which accompanied it and the mortality rate were, however, unprecedented.

It is well to recall that the autumnal outbreak of that year did not arrive unheralded. In the winter of 1915-16 an extensive epidemic took place. The influenza of the spring and summer of 1918 differed in no essential feature from that of recent years. Furthermore, practically all observers refer to the uncomplicated cases in the autumnal wave as 3-day fevers and it should be remembered that they constituted 80 to 90 per cent of the total in 1918. In other accepted pandemics the percentage of complications was extremely low, even though the incidence of disease was high. Thus, the term, pandemic, is not synonymous with high mortality.

It is my firm belief that the epidemics of varying extent which occur from year to year are the typical disease and that an episode such as that of the fall of 1918 represents a bizarre occurrence due probably to a simultaneous visitation of virulent influenza virus and a widespread dissemination of highly invasive bacteria of various species. Hence, the results of recent investigations, seeking insight into the accepted and debated opinions, appear applicable to the problem of influenza as a whole.

MEASURES TOWARD PROPHYLAXIS OR THERAPY

Early in the course of virus studies attention was attracted by the fact that when large doses of active influenza virus were given to experimental animals by routes other than the intranasal, characteristic infection did not occur. Nevertheless animals developed antibodies and became immune to virus given by the usual mode of inoculation. Furthermore, Shope¹⁵ demonstrated with swine influenza virus that intracutaneous vaccination elicited an excellent antibody response and that when such animals were subsequently infected intranasally they were protected against pulmonary invasion even though a febrile

reaction and some nasal signs developed. These results have been amply confirmed with human strains. Furthermore, it has been practically impossible to recover virus from animals so treated, showing that vaccination increases the capacity to dispose of the infectious agent. These observations suggested that a similar series of events might be induced in man. In 1935 we conducted experiments to test this hypothesis.¹⁶ It was found that the subcutaneous injection of relatively large amounts of active virus did not induce clinical infection in human subjects but that a sharp rise in circulating antibodies occurred. Since a rise in antibodies occurs as a result of infection and is associated with the immunity of convalescence, it seemed probable that the rise which followed vaccination also indicated the development of an increased resistance.

In this country an evaluation of subcutaneous vaccination of active virus as a measure protective against the natural disease in man has been attempted by Stokes and his associates^{17, 18} and by Siegel and Muckenfuss.¹⁹ The results have not justified a straightforward conclusion. In 1936 the figures obtained by Stokes and others, suggested a beneficial effect but subsequent studies have not been easily interpreted. Siegel and Muckenfuss in 1938-39 failed with the material they used to observe a satisfactory antibody response and, as would be expected, no statistically significant protection was noted. Thus, the procedure has not proven itself and the results so far have not been conclusive enough to permit any verdict. Under proper conditions, involving the use of a sufficiently good virus preparation to function as a proper antigen, and the coincidence of a well established outbreak of epidemic influenza in the test community, evidence will be gained, but not otherwise.

In England a vaccine of formolized inactive virus has been shown by Andrewes and Smith²⁰ to give rise to immunity in mice inoculated intraperitoneally and also to induce the formation of antibodies in human subjects. Nevertheless, the immunity has not been as firm as that produced by active virus. The results of its application to man have yielded no indication of protection against the natural disease.

More recently, Horsfall and Lennette²¹ have reported the enhancement of immunity to influenza, in ferrets vaccinated with mixtures of inactivated influenza and canine distemper viruses. This interesting phenomenon is being intensively studied.

Despite the lack of information there has been a lurking suspicion that the subcutaneous injection of active virus would not be entirely

satisfactory under the most careful conditions. After all, it is clear that ferrets do not develop a complete immunity, and even in mice the resistance acquired as a result of subcutaneous vaccination is never as great as that which follows intraperitoneal immunization. Because of this we have been led to further consideration of the use of the nasal route for prophylactic procedures. The fact that subclinical infection in epidemic periods is common and the fact that the mere presence of antibodies is not synonymous with immunity have been well established. It seemed not unlikely that agents active in the nose might be important factors in determining clinical response since this is the primary point of attack of influenza virus. Together with Stuart-Harris²² it was demonstrated that ferrets recovering from virus infection developed a new type of transitional-squamous epithelium which was resistant not only to virus but to severe physico-chemical injury with zinc sulphate ionization as well. Unfortunately, the change was not a permanent one but the respiratory mucous membrane was so conditioned that repair following reinfection was markedly accelerated. The possibility exists that changes of this sort bear some relation to the variations in resistance of different individuals and that these modifications could be influenced and maintained by nasal vaccination.

In addition, studies in our laboratory²³ and that of Burnet²⁴ have revealed that the nasal secretions of human subjects may contain a substance capable of inactivating relatively large amounts of the virus of epidemic influenza. A wide variation in the inactivating capacity is seen in the secretions at different ages or in different individuals of the same age. Since both the cellular factor and this serological factor are resident in the nose where the virus initiates infection, it may be that the local introduction of virus antigen by stimulating these mechanisms might produce more benefit than would accrue from simply increasing antibodies in the general circulation. Experiments to investigate these possibilities are being carried on at the present time. It has been found that as much as 10,000 mouse-lethal doses of virus cultivated in tissue culture medium can be given intranasally to human subjects without producing infection.²⁵ To what extent immunity develops has not yet been ascertained. It may be that only those whose nasal secretions are devoid of virus-inactivating substances need be subjected to immunizing procedures.

While it is apparent from this recital that prophylaxis against the

virus of epidemic influenza in man is in the experimental stage, the outlook on theoretical grounds appears quite promising. The procedures which are being carried out have a firm and clear-cut foundation in the results of animal experimentation. One difficulty which I do not propose to discuss at present is that strains of the virus may differ. If, however, an effective method of producing immunity against any one strain is established, the rest will follow. As previously stated, one of the chief obstacles to proper evaluation is the lack of cooperation on the part of the disease itself, in not presenting itself in the desired spot at the desired time.

Thus, while attempts to devise a satisfactory prophylactic procedure are being carried out, other efforts are also going on which may have a bearing on clinical therapy of epidemic influenza. It has been shown repeatedly that the injection of potent immune serum intraperitoneally into mice will give excellent passive immunity. More recently, Smorodintseff,²⁶ and Stokes, Henle and Shaw²⁷ have reported the fact that when the serum is given by the intranasal route even as late as 24 to 48 hours after infection of mice, fatal outcome may be prevented. These indications are suggestive. Certain clinical observations of 1918 also contain hints that convalescent serum may be of benefit.

On the other hand, chemotherapeutic agents have given no indication up to the moment of exerting any curative or prophylactic effect upon the virus disease in experimental animals. Since, however, the evidence points to the fact that the fatalities in epidemic influenza are to a great extent dependent upon bacterial complications, I believe that chemical therapy will be of tremendous value in controlling mortality.

In the presence of a highly virulent virus which of itself would produce a great incidence of pneumonia the outlook would be more problematic. Up to the present, rest, isolation and respiratory comfort have not been supplanted. Probably the most valuable factor in the control of epidemic influenza is increased emphasis on respiratory hygiene, if any such thing exists.

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THE RICKETTSIAL DISEASES, WITH SPECIAL REFERENCE TO THOSE OF IMPORTANCE ALONG THE ATLANTIC SEABOARD*

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GENERAL CONSIDERATIONS

SINCE the beginning of the bacterial era toward the end of the Nineteenth Century, two new and important groups of microscopic pathogens have been discovered, the viruses and the rickettsiae. The rickettsiae, which we are to discuss tonight, have some of the characteristics of ordinary bacteria and some of the attributes of viruses, and there are many bacteriologists who regard them as intermediate between these two forms. In order to understand the diseases which they cause, it is desirable to begin this talk with a brief survey of their life history.

While some of the rickettsial diseases have been known for centuries, the rickettsiae themselves were probably seen first by the brilliant young American bacteriologist, Howard Taylor Ricketts, during his studies of Rocky Mountain spotted fever. After his death from typhus fever, they were named in his honor by da Rocha-Lima, in 1916. Since their discovery the rickettsiae have been intensively studied, and while there are still many gaps in our knowledge concerning them, much has been learned regarding their life history.

Rickettsiae are found all over the world. So far as we know there is no country, civilized or uncivilized, in the temperate and tropical zones in which they do not flourish. Under natural circumstances their hosts are insects and, what is important from the point of view of human disease, many of these are insects which invade and bite man, such as lice, fleas, ticks and mites. However, actual biting is not always necessary, as soiling of the skin by crushing the insects may transmit certain of these diseases. Some rickettsiae are pathogenic both to man and to their insect hosts, some are pathogenic to man but not to the insects which transmit them, while many are harmless to both insects and man.

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Many rickettsiae are able to live and flourish in animals, particularly rodents, but also dogs, rabbits, deer, squirrels, woodchucks, opossums, and many other vertebrates. In invaded animals, as in man, the rickettsiae are carried by insects, notably by fleas and ticks, and in animals also the rickettsial infections may be either clinically inapparent or may result in demonstrable illness. The importance of animal infection lies in the fact that infected animals may serve as reservoirs of rickettsiae during inter-epidemic periods.

Morphologically rickettsiae are smaller than most bacteria. They resemble small cocci or bacilli or may occur in filamentous forms. Variability in form is one of their outstanding characteristics. The bacillary forms average from 0.3 to 0.5 of a micron in length and about 0.3 of a micron in width, but some of them are 6 or 7 times the average length. Rickettsiae are not as readily stained as ordinary bacteria, they decolorize by Gram's method and they stain best with Giemsa's stain or the buffer-formol dyes of Castaneda. Most of them are non-motile and are readily destroyed outside of the body by heat, drying or bactericidal chemicals. They cannot be grown on ordinary culture media but some of them grow quite luxuriantly on media containing fragments of animal tissue containing viable cells. Most of the pathogenic rickettsiae are host-specific, which means that they are always transmitted to man by the same type of insect vector. Furthermore they are more or less tissue-specific and the pathogenic rickettsiae are always intracellular.

Pathology. A brief summary of the pathological lesions common to most rickettsioses is desirable because of its bearing on the clinical picture. The essential damage in practically all rickettsioses is to the blood vessels and the extent of this damage depends upon the character and virulence of the particular rickettsial infection. In the Rocky Mountain spotted fever group, for example, the media of the vessels is mainly affected and, as a consequence, a hemorrhagic skin eruption followed by local skin necrosis, and necrotic lesions of the fingers, toes, ear lobes, scrotum and penis are not infrequent. In typhus fever in which the intima of the vessels is chiefly involved, there are similar but less severe hemorrhagic and necrotizing lesions. In both these groups involvement of the vessels of the brain explains the severe nervous phenomena which are so common in most rickettsial diseases.

Classification of the rickettsioses in the light of existing knowledge, is difficult for several reasons. The following are the most important

1 Those who have attempted to classify the rickettsioses have often failed to employ a sufficient number of differential criteria. Not only must the clinical features of the diseases be considered, but the morphology and cultural characteristics of each organism, its immunological reactions, its gross and microscopic pathology, and the effects of its inoculation into animals must also be taken into account.

2 Confusion has been caused by the fact that the same disease has been described by different names, i.e., there are local names which are misleading. Thus the Sao Paulo typhus of Brazil is not typhus fever but Rocky Mountain spotted fever.

3 Confusion has also been caused by the fact that the epidemic and sporadic types of some rickettsial infections show such tremendous differences in mortality that it is hard to believe they were the same disease and also by the fact that, contrasted with bacterial diseases, rickettsial infections show a much wider divergence in symptomatology.

There are three main groups of rickettsial diseases, viz (1) The typhus fever group, (2) The spotted fever group, and (3) The Japanese River fever group. There are, in addition, three diseases, two of which are undoubtedly rickettsial, which have not yet been satisfactorily classified. One of these is the Australian Q disease, another is Weigl's disease, a purely laboratory infection, and the third is trench fever, which Wolbach does not think is caused by true rickettsiae and which has disappeared since the war of 1914-18. None of these is of importance in this country at present.

There are certain features common to most rickettsiae which may be outlined before discussing the individual diseases in which we are particularly interested. Briefly, these are

- 1 Transmission by insect vectors
- 2 A primary sore at the point of inoculation in some rickettsioses (Tsutsugamushi, South African tick-bite fever, boutonneuse fever)
- 3 A clinical course usually beginning suddenly and violently, a hemorrhagic skin eruption, marked involvement of the central nervous system and a high fever which terminates by crisis.

The two groups of rickettsial infection which are important to those of us who practice along the Atlantic Seaboard are the typhus fever group and the Rocky Mountain spotted fever group. These will now be discussed.

THE TYPHUS FEVER GROUP

Clinicians long confused typhus and typhoid fever though works written in the Eighteenth Century, such as Huxham's book on fevers and Langrish's Practice of Medicine, do distinguish between slow, nervous fever, which we call typhoid, and malignant, or putrid malignant fever, which is typhus. It was not until the Nineteenth Century that a clear differentiation, on clinical lines of course, was established by two former students of P. C. A. Louis: Gerhard and Pennock of Philadelphia. We now recognize two forms of the disease, (1) the epidemic and (2) the sporadic or murine type.

The *synonyms* which have been applied to typhus fever are almost innumerable, Murchison lists over ninety of them. Many of them are based on clinical features, such as the skin eruption or the effect on the nervous system, but the most illuminating are those which clearly foreshadow the association of the disease with famine, overcrowding and unsanitary conditions: ship fever, jail fever, camp fever, famine fever.

The *geographical distribution* of typhus fever is world-wide. There is no country either in the Old or the New World which has not, at some time, suffered from the scourge. Under normal conditions there has been a tendency in civilized countries for large epidemics of the disease to disappear. Under abnormal conditions, such as those which accompany the present war on the continent of Europe, the epidemic form of the disease has already developed and is likely to continue until conditions return to normal.

So far as the *etiology* of the disease is concerned the preceding discussion has already indicated the chief *predisposing causes*, viz. famine and overcrowding, conditions which lower individual resistance and favor the spread of lice from one person to another. It is to be noted that both the head louse and the clothes louse can carry the infection and that the lice themselves are killed by it. The *exciting cause* of the Old World type of epidemic typhus is *Rickettsia prowazekii*, a small, non-filterable bacterium-like body which is found in the intestinal epithelial cells of the louse. The organism is at times demonstrable in the circulating blood of typhus patients but is present chiefly in the endothelial cells of the blood vessels. It can be successfully grown on media containing tissue especially the guinea pig tunica-agar-horse-serum medium of Zinsser and his associates. The exciting cause of New World epidemic typhus or tabardillo is the *Rickettsia mooseri* and sporadic or murine typhus may be

caused by either the Old World or the New World virus

Symptomatology The clinical picture of Old World epidemic typhus is indistinguishable from that of tabardillo, the New World type. The period of incubation is apt to be somewhat shorter in the New World type. The average period of incubation of epidemic typhus is nine or ten days. During the period of incubation the patients are usually symptom-free, although a small percentage complain of malaise, slight headache, vertigo and loss of appetite for a day or two before the real onset of the disease. The symptoms of onset are apt to appear with abruptness and violence. There may be a rigor with severe headache and backache, a "bruised sensation" in the limbs, anorexia, fever and at times sweats and great thirst. Nausea is occasional but signs of acute gastrointestinal irritation are usually lacking. Restlessness, tinnitus, vertigo and insomnia, signs of involvement of the central nervous system, are often present from the onset. Deafness is not infrequent. As compared to typhoid fever the symptoms in typhus increase in severity much more rapidly so that at the end of the first week a typhus patient may look like a case of severe typhoid at the end of the second week. Signs of toxemia in the form of persistent, intense headache, confusion or even stupor, muscular twitching and exhaustion are common by the end of the first week. The rash usually appears on the fourth day but may not appear till the seventh. The headache may subside at the beginning of the second week and is often replaced by violent delirium, at times accompanied by suicidal tendencies. Increasing prostration develops as the disease progresses and the patient may become stuporous towards the end of the second week and continue in this condition until the sixteenth or seventeenth day when, if recovery is to take place, sudden improvement occurs with a drop in the temperature and sometimes with a critical sweat or critical diarrhea. In uncomplicated cases the mental condition clears in a few days, the appetite returns and convalescence is quickly established.

The striking things about the physical examination are, (1) the signs of severe toxemia with nervous involvement—the dull, heavy expression, the injected conjunctivae, the dry, brown, tremulous tongue and the muscular twitchings, and (2) the rash. This varies in appearance in different stages. It evolves as a continuous succession of lesions over a period of several days. It is apt to appear first on the anterior axillary folds and the sides of the abdomen and gradually involves the back and ex-

tremities, including the backs of the hands and the dorsa of the feet. *It usually spares the face and neck.* At the outset it is measly looking and consists of irregular, roughly rounded or oval, elevated areas of macular erythema, isolated or grouped, and varying in color from dirty pink to bright red. These disappear on pressure except in the rare cases where the rash is hemorrhagic from the onset. In most cases the rash darkens in shade and does finally become frankly hemorrhagic. It usually persists until the febrile crisis and then fades gradually.

The *fever* in epidemic typhus is usually rather high from the beginning and may reach $F\ 104^{\circ}$ by mouth, even on the first day. It often reaches its maximum by the time the eruption appears toward the end of the first week. At the height of the disease it often ranges between $F\ 103^{\circ}$ and $F\ 105^{\circ}$ in an average case, and in a severe case it may range between $F\ 104^{\circ}$ and $F\ 107^{\circ}$. The daily variation is usually not more than two degrees and as a rule the increase in the pulse rate parallels the fever. As the temperature falls towards the end of the second week the daily range of temperature becomes greater and as a rule a crisis occurs on the fourteenth to the eighteenth days.

In uncomplicated cases there is little to be made out on physical examination except the signs already described. However, there are certain complications which are fairly frequent, such as acute bronchitis and bronchopneumonia. Before good nursing and care of the mouth were customary, parotitis was a common complication, and in severe epidemics it is usual to have gangrene of the extremities.

The *laboratory findings*, with the exception of the Weil-Felix reaction, can hardly be described as pathognomonic. The urine shows nothing but the ordinary febrile changes. The blood picture varies with the stage of the disease and the severity of the infection. Some writers state that leukopenia is usual until the rash appears, after which there is a leukocytosis with an increase in the polynuclear ratio. While this may be the rule, there are some patients who, from the onset, show leukopenia and a polynuclear ratio as low as 20 per cent.

The so-called *Weil-Felix agglutination reaction* in typhus fever occurs with *Proteus* OX 19 and may appear as early as the fifth day. In order to confirm the diagnosis of typhus fever an agglutination titer of at least 1 to 50 is necessary. During the period of maximum intensity, which occurs two to three days before the crisis, titers as high as 1 to 2500 may be found, and some agglutination may persist for several

months after the attack is over

The *diagnosis* of epidemic typhus is not usually difficult except at the beginning of an outbreak, especially if this occurs in a location that has not been visited by the disease for many years so that many physicians may never have seen the disease. The history of infestation with lice, the sudden and violent onset, the character and distribution of the eruption, the marked involvement of the central nervous system and the duration of the fever with termination by crisis constitute a distinctive group of symptoms and signs. Before the eruption appears the disease has been mistaken for meningitis, influenza, smallpox and other severe infectious fevers.

The disease which was formerly confused with typhus fever was *typhoid fever*, but the more gradual onset, the much less profuse skin eruption with its different distribution and character, the positive Widal reaction, and the lack of any increase in leukocytes in typhoid fever should leave no doubt as to the distinction.

In children *measles* may cause confusion, although typhus fever is not preceded by any period of upper respiratory catarrh, and children with typhus fever are very much sicker than children with measles as a rule. There are of course no Koplik's spots in typhus fever and the blood picture is quite different in the two diseases.

In many places more than one type of rickettsial infection may be present at the same period. This is true in the eastern United States, where typhus fever and Rocky Mountain spotted fever both occur. The differentiation between the two will be discussed under Rocky Mountain spotted fever.

Prognosis There is a great deal of variation in the mortality from epidemic typhus fever in different epidemics and in different regions. In South Africa the average mortality is only about 13 per cent and is much lower in the whites than it is in the negroes. In the New York epidemic of 1893 there was a mortality of 44 per cent. As high as 70 per cent mortality has been reported in some epidemics.

The chief factors influencing mortality are (1) the mass reduction of resistance by inanition and unhygienic surroundings, (2) age is very important in children the mortality seldom reaches 5 per cent, after the age of 65 it is generally over 80 per cent, (3) the mortality is generally higher at the beginning than it is at the end of an epidemic, and (4) the presence of complications, particularly bronchopneumonia or peripheral

gangrene adds tremendously to the mortality. Obesity, chronic alcoholism and preexisting chronic disease also increase the mortality.

Prevention Inasmuch as the epidemic form of typhus fever is always transmitted by lice, the obvious method of control is to prevent the infestation of human beings by these parasites. In the case of physicians or nurses, the avoidance of louse infestation is a simple problem. Some form of protective covering must be worn. The protective clothing must be composed of some smooth, hard material, of narrow mesh, which is impermeable to lice, and must take the form of a one-piece overall which includes the feet and which can be rendered impenetrable at the wrists and neck. In addition there must be some form of hood which protects the scalp and neck but permits vision.

Inasmuch as epidemic typhus often attacks areas containing congested populations, the problem of wholesale delousing is the most important one in the control of the disease. In the case of troops, systematic bathing and hair cutting with sterilization of clothing can be enforced as a military order. Both lice and rickettsiae are destroyed by moist heat at 70° centigrade for 30 minutes, or dry heat at 55° centigrade for 5 minutes. The wholesale delousing of civilian populations is seldom entirely satisfactory although it has been carried through with some success. Among savage or semi-civilized tribes the problem is even more difficult.

The most satisfactory method of controlling typhus fever in areas where it is at times epidemic is *preventive inoculation*. No doubt the efficiency of this procedure will be tremendously increased by the discoveries of Zinsser and his associates, who have been able to devise methods of growing rickettsiae in large amounts. The method of Weigl in which a vaccine was produced by using lice as culture media and making a suspension of their centrifugalized and triturated gastrointestinal canals, has been successfully used, but the process is so expensive and time-consuming that the method cannot be used on a large scale.

MURINE TYPHUS

So far as the physicians of this part of the world are concerned murine typhus is much more important than the epidemic type for while we have not had an outbreak of epidemic typhus in the eastern states for many years, the murine type is constantly present. The name "murine" was given to this form because it has been shown that it is trans-

mitted by rat fleas Zinsser believed that the murine typhus of New York City might be due to recurrences in adults who had previously had the disease The researches of Maxcy lend support to the view that the contamination of food by rats and mice may also be a source of the murine type In New York City this form of typhus has long been known as Brill's disease because the late Nathan Brill was the first to point out its prevalence in this region

There are a number of points of difference between the epidemic and murine forms of typhus which may be summarized by stating that the murine type is much less severe as a rule The mortality of the two forms is entirely different In this country it is probably from 1 to 1½ per cent in murine cases but there are other parts of the world, Tunis, for example, in which the mortality may reach as high as 10 per cent The period of incubation and the onset of the disease do not differ materially in the murine and epidemic forms, although the onset is often less violent in the murine form The course of the disease tends to be a little shorter in the murine form and in most patients the fever falls by crisis at the end of the second week The patient is not so seriously ill in the murine form and the skin eruption is less profuse and much less apt to be hemorrhagic The Weil-Felix reaction occurs with *Proteus* OX 19 just as it does in epidemic typhus

It is obvious that, as the method of transmission of murine typhus is different from the method of transmission of epidemic typhus, the preventive measures are different In Tunis preventive inoculation has led to a marked reduction in morbidity In this country the cases are few in number and widely scattered among large masses of people Preventive inoculation is, therefore, not a practical solution The only other means of prevention involves rodent extermination and the rat-proofing of buildings, especially those in which food is stored The extermination of rodents on a large scale is a very expensive procedure and would certainly not be justifiable on the ground of typhus prevention alone It is possible that if one considered also the losses incurred by farmers and food dealers from rats there might be justification for campaigns against rodents under certain circumstances Prevention of human contact is not necessary in murine typhus and patients may safely be treated at home

Treatment Little need be said regarding the treatment of typhus fever There is no specific treatment It is possible that experience may show that some of the modern bactericidal drugs are of value In brief,

typhus patients are treated symptomatically along the lines that are followed in any febrile infectious disease. Good nursing and good surroundings, free administration of fluids, adequate food supply, and the care of the emunctories constitute the important steps.

THE SPOTTED FEVER GROUP

The only member of the spotted fever group which we need to consider here is Rocky Mountain spotted fever. The name suggests that the disease is limited to the region of the Rocky Mountains but the experience of recent years has shown that it occurs in every part of the country, although there are a few states from which it has not yet been reported.

Rocky Mountain spotted fever may be defined as a specific tick-borne infection due to *Rickettsia rickettsi*, characterized pathologically by proliferative, degenerative and thrombotic lesions in the peripheral and testicular vessels, and clinically ranging in severity from mild and ambulatory to fulminating and fatal infections, having in the average case a sudden onset with evidences of severe toxemia and a maculopapular rash.

There are two main types of the disease, the Eastern and the Western.* The Eastern type is transmitted by the common dog tick, *Dermacentor variabilis*, and the Western type is most commonly transmitted by the wood tick, *Dermacentor andersoni*, occasionally by the rabbit tick, *Haemaphysalis leporis-palustris*. It is important to point out that the dog tick may be carried by animals other than the dog. It has been found occasionally on horses and cattle, on rabbits, deer, wildcats, foxes, squirrels, opossums, badgers, coyotes, skunks, wolves, asses, hogs, woodchucks, and weasels. The wood tick too may be found on various kinds of deer, on mountain goats, horses, mules, asses, cattle, dogs, badgers, rabbits, woodchucks, prairie dogs, wildcats, hogs, porcupines and coyotes. The rabbit tick may be found on birds and can be carried by them for considerable distances.

Infection of ticks with the rickettsia of Rocky Mountain spotted fever does not result in the destruction of the insect. On the contrary, the ticks are able to transmit the rickettsiae from one generation to another and this ability and the fact that various animals can act as hosts

*The Minnesota strain described by Reimann and his associates appears to be a localized mild variety of the Western type.

to the tick account for the keeping alive of the infection during inter-epidemic periods. Only a small percentage of ticks are infected.

Etiology The chief predisposing cause in the Western type is occupation. Shepherds, cattlemen, hunters and trappers, prospectors, foresters, section hands, road builders and surveyors are especially liable because their work takes them into *wooded country where the ticks are common*. Children are frequently victims of the Eastern type because of their intimate contact with dogs.

The *exciting cause* of Rocky Mountain spotted fever is undoubtedly the organism observed by Ricketts in 1906. Wolbach's classical researches thirteen years later led to the detailed description of the parasite which he named *Dermacentor venus rickettsi*. Wolbach showed that the parasite, usually in lancet-shaped forms, can be demonstrated in the vascular lesions of the disease. It has since been rechristened *Rickettsia rickettsi* and has been grown successfully on tissue cultures by a number of bacteriologists.

Symptomatology The incubation period of the disease varies somewhat according to the severity of the infection. In the mild cases Parker gives the incubation period at from 3 to 5 days, in the severer ones from 3 to 14 days. During the incubation period a few patients show anorexia, malaise and irritability, but usually the onset of the attack is sudden.

The disease frequently begins with a distinct rigor accompanied by fever and sweating, and commonly with severe headache, backache, and limb aches. Prostration is common from the beginning of the disease and evidences of involvement of the nervous system in the form of photophobia and stupor are also common. Nausea and vomiting occasionally occur at the onset. As in typhus fever, the symptoms usually increase rapidly in intensity and with this rapid increase the nervous symptoms become more marked. Delirium, muscular twitching or even incoordination, restlessness, insomnia, stupor and even coma and convulsions may be present. Examination of the patient at this stage shows a flushed and often apprehensive facies, cyanosis, a palpable spleen, and (according to Parker) frequently a distinctive odor. There may be evidences of meningism and even ankle clonus and the Babinski phenomenon have been noted occasionally. The characteristic rash usually appears from the second to the fourth day but may be delayed until the fifth or sixth day. It is a macular or maculo-papular eruption, at first pink and dis-

appearing on pressure, but gradually becoming darker, bluish rather than pink, and no longer disappearing on pressure. In the milder cases it may come out in crops, in the severe ones it is apt to be hemorrhagic and confluent. It generally appears first on the wrists and ankles, later on the forehead and back, and finally may involve the entire body including the scalp. There is often an enanthem on the mucous membrane of the mouth. After recovery, pigmented areas which become congested on exertion or exposure may remain for some time.

The fever usually lasts for two or three weeks but is not as fixed in duration as the fever of typhus or typhoid fever. In the average case temperatures above $F\ 103^{\circ}$ are rather uncommon. In severe cases the temperature frequently reaches $F\ 105^{\circ}$ early in the disease and in fatal cases may go as high as $F\ 108^{\circ}$. The maximum temperature usually is reached by the end of the first week and is apt to persist through the second week when a fall by lysis usually begins. Parker notes a difference in the duration of the lysis according to the transmitting tick. Strains transmitted by *Dermacentor andersoni* occupied 7 to 8 days for the period of lysis, while those transmitted by *Dermacentor variabilis* only occupy 3 or 4 days.

The ordinary laboratory examinations are not particularly helpful in the diagnosis of the disease. The urine simply shows the usual febrile changes. The blood picture is not characteristic as there may be either a mild leukocytosis, not above 15,000 per cubic millimeter, or a leukopenia. The Weil-Felix reaction in this disease varies but there is usually agglutination of both *Proteus* OX 19 and *Proteus* OX 2. In doubtful cases the infection test and the virus neutralization or protection test may be used to substantiate the diagnosis.

Convalescence is apt to be slow even in patients who have had a mild attack and a complete return to normal may occupy a good many months.

The complications of the disease are those which are apt to occur in almost any infection: pulmonary inflammatory lesions, phlebitis, acute nephritis and occasionally secondary streptococcic sepsis. The deep gangrenous lesions which may complicate typhus fever are generally absent although there may be superficial sloughing of the genitalia and the dependent parts of the body in some patients.

Diagnosis. In this region the chief diagnostic problem is the differentiation of Rocky Mountain spotted fever from the murine form of

typhus There is no marked difference in the onset, though chills are more common in Rocky Mountain spotted fever and headache more prominent in murine typhus The fever in Rocky Mountain spotted fever lasts longer than that of murine typhus The distribution of the rash is different in the two diseases, as has already been pointed out Murine typhus serum agglutinates *Proteus* OX 19 only, while Rocky Mountain spotted fever serum also agglutinates *Proteus* OX 2 The Eastern type of Rocky Mountain spotted fever is more common in children while murine typhus is more common in adults The rat is the only animal reservoir for the virus of murine typhus while many animals may probably serve as reservoirs for the virus of Rocky Mountain spotted fever The rat flea is the vector of murine typhus while the dog tick is the vector of the Eastern type of Rocky Mountain spotted fever Murine typhus is usually a disease of cities while Rocky Mountain spotted fever is usually contracted in the country Murine typhus has a mortality of less than 1 per cent while Rocky Mountain spotted fever has one of about 25 per cent on the average

Prognosis A good many writers state that the Western type of the disease is much more fatal than the Eastern type As a matter of fact the mortality of the Western type shows tremendous local variations The areas of high case mortality are quite sharply defined and the majority of patients with the Western type suffer from mild to moderately severe attacks Hampton and Ewbank show that from 1933 to 1937 the mortality in the Pacific states was 19.4 per cent, whereas in the Southern states it was 18.1 per cent The number of cases which have been reported from the northeast is still so small that one cannot base any conclusion as to mortality upon them

Prophylaxis The prevention of the disease in the East, where the disease is carried by the dog tick is somewhat different from prevention in the Western states where it is carried by the wood tick So far as the Western type is concerned it is to be noted that control of ticks by wholesale extermination of wild animals is hardly a practicable measure The obvious preventive measure is the protection of the body against the attachment of ticks in all whose occupation takes them into tick-infested areas As most ticks become attached on the lower leg the protection of legs by high boots, long socks, leggings or puttees is the most important thing Women tramping in infected areas should wear trousers and should protect their legs just as men do If the legs are

protected, ticks can only gain access to the body by crawling up clothing, where they may often be seen and removed. If unobserved they may gain access to the arms, especially if the sleeves are rolled up, and to the neck, where they are frequently felt and promptly removed. Persons in tick-infested areas should remove all their garments before retiring for the night and should make a careful inspection of the body. In women it is particularly important that the hairy scalp be inspected. If ticks are found they should never be crushed but should be carefully removed by the fingers or a pair of tweezers by gently pulling on the tick so as to elevate the skin surrounding the area of attachment, and then prying loose the tick from the hypoderm with a hypodermic needle or the point of a scalpel. The small wound thus produced should be touched with a nitrate of silver stick or tincture of iodine. In the East where the disease is transmitted by the dog tick the problem of avoidance is different. Dog owners in districts where ticks are prevalent should be educated to keep their dogs free from ticks.

Individuals who live in known infected areas and whose occupation takes them into wooded regions should be subjected to *prophylactic vaccination*. The United States Public Health Service furnishes a vaccine which is prepared at the Rocky Mountain Laboratory of the National Institute of Health at Hamilton, Montana, and is distributed from this point. At the present time the technique involved in the preparation of this vaccine is difficult, the amount which can be prepared is limited, and the vaccine is therefore expensive. It is to be hoped that with the new methods of cultivation which have been developed it will be possible to produce a vaccine in large quantities by much simpler and less expensive methods. Inasmuch as the protection furnished by the vaccine lasts only one season, annual inoculation is necessary.

Treatment The treatment of Rocky Mountain spotted fever, like the treatment of typhus fever is symptomatic and is essentially the same for the two diseases.

Those who have given any study to the subject are well aware that there are many aspects of the rickettsioses which have been left undiscussed. The question of the relation of rickettsial infection to proteus infection, the details of the serology and immunology, the whole question of the experimental production of these diseases have been barely touched upon. In the time at our disposal it was possible to

emphasize only certain phases of the problem, particularly the practical situation as it applies to this part of the country. If you are desirous of obtaining more information, you can get this from monographs such as the recent work on virus and rickettsial diseases published by the Harvard University Press.*

* *Virus and rickettsial disease. Symposium held at the Harvard School of Public Health, Cambridge Mass., Harvard Univ. Press, 1940. 907 pp., illus.*

STUDIES ON CHORIOMENINGITIS AND POLIOMYELITIS

Harvey Lecture, October 31, 1940

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CENTRAL nervous system ailments known to be or suspected of being caused by viruses are apparently on the increase and they constitute a puzzling diagnostic problem for the clinician

For instance, a group of cases characterized by fever with symptoms of meningeal irritation and a clear to slightly turbid, sterile-to-culture spinal fluid showing a lymphocytic cellular response has been considered as a clinical entity under such varied designations as lymphocytic or aseptic or idiopathic meningitis. Laboratory investigators have now split certain etiological entities such as lymphocytic choriomeningitis and pseudolymphocytic choriomeningitis from this group of cases, but there still remains a residue of cases of unknown etiology.

These developments denote progress, yet I fear that the development of an etiological classification has rendered the clinician's problem more complex, since, in the individual case of central nervous infection, an etiological diagnosis is usually not possible on clinical findings alone but must rest upon laboratory determinations. It is by this fact that I would justify this essentially laboratory presentation of certain aspects of lymphocytic choriomeningitis and of poliomyelitis.

LYMPHOCYTIC CHORIOMENINGITIS

The virus of lymphocytic choriomeningitis was first isolated and described in 1934 at the National Institute of Health.¹ The virus was first isolated with certainty from a human case by Scott and Rivers in 1935 and has subsequently been isolated from widely separated portions of the United States²⁻⁷ and in England,¹⁰ France¹¹⁻¹² and

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Japan¹³ and in northern Africa,¹⁴ and there is clinical and serological evidence of its presence in Ireland¹⁵ There are, moreover, reasons for feeling that the virus is probably world-wide in distribution

The symptoms as described for etiologically proven cases of choriomeningitis have varied markedly although the viruses isolated therefrom have been immunologically similar with the exception that MacCallum, Findlay and Scott¹⁶ studied two cases which clinically resembled choriomeningitis from which identical strains of virus were isolated These viruses simulated choriomeningitis in both their clinical and pathological manifestations in experimentally inoculated monkeys and mice, but were found to be immunologically distinct from choriomeningitis and were designated as the virus of pseudochoriomeningitis

Symptomatology A sufficiently large number of proven cases of choriomeningitis virus infection have not as yet been observed to assure that all the clinical manifestations of the disease have as yet been identified However, several clinical types of the disease are now known to exist

1 *A grippal or non-nervous system type* Many persons who deny having had any central nervous system ailment whatever have been found to harbor specific virus-neutralizing antibodies in their serums, which suggests the occurrence of a systemic type of infection without central nervous system involvement This assumption is supported by the fact that susceptible animals, when inoculated with the virus by routes other than directly into the central nervous system, usually develop symptoms without evidence of meningeal or brain involvement, and French investigators¹⁷ have shown the same to be true for human volunteers inoculated subcutaneously with the virus That such human cases also occur in nature has recently been demonstrated at the National Institute of Health¹⁸ where the first spontaneously acquired case of this systemic type yet reported¹⁸ was observed The case occurred in a 31 year old man engaged in choriomeningitis research On March 11, 1940, he developed moderate fever with troublesome pains in his arms and back (Fig 1) During the next three days his fever increased to 38.8° C but anorexia, malaise, marked prostration, and lumbar pains so severe as to require codeine were his only complaints His face was somewhat flushed but otherwise the physical examination was negative There was no headache, or stiffness of the neck or altered reflexes A blood count on the fourth day of illness revealed 2900

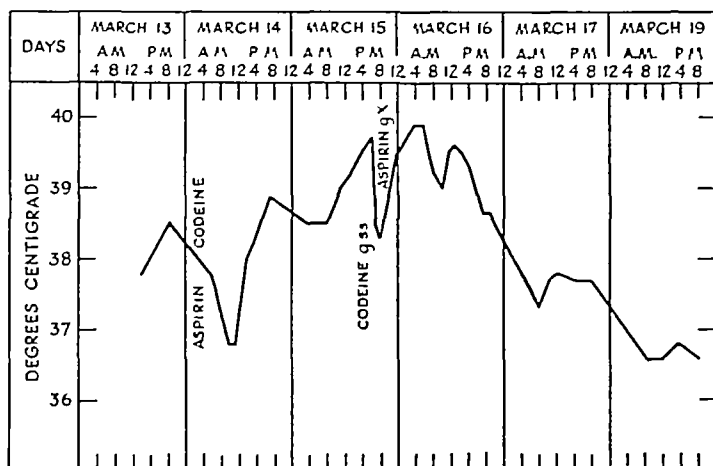


Fig 1—Temperature course in patient with systemic choriomeningitis virus infection without central nervous system involvement

white cells of which 45 per cent were polymorphonuclear neutrophils, 50 per cent lymphocytes, and 5 per cent mononuclear cells. On the fifth day of illness his temperature reached its height 39.9°C and there was marked prostration and backache. The next day the fever was lower and his temperature reached normal on the seventh day accompanied by marked amelioration of the pains. Weakness and prostration were marked, however, and persisted for a full week following the return of his temperature to normal. The clinician in charge considered the case to be one of uncomplicated influenza.

There was no indication for a spinal tap and none was done. Blood drawn on the fifth day of illness and inoculated into white mice induced the typical clinical and pathological picture of choriomeningitis and the virus was immunologically identified. Blood drawn in November, 1939 was negative when tested for specific antibodies, while a sample drawn on April 28, 1940 was markedly protective.

This identification of an influenza-like ailment due to the virus of choriomeningitis is of interest in view of the fact that approximately 11 per cent of 2000 sera collected at random from various parts of the United States contained antibodies for this virus, but with rare exceptions the donors when interrogated denied any history of central nervous affection. It is possible therefore that a portion of the cases of

"grippe" or "influenza," especially in interepidemic periods may be due to the virus of choriomeningitis

2 *Meningeal type* The central nervous system symptoms are often preceded by upper respiratory or influenza-like manifestations which usually improve, to be followed in several days by the sudden appearance of fever with meningeal symptoms such as severe headache, vomiting, stiff neck, and by positive Kernig and Brudzinski signs. The spinal fluid is clear, sterile-to-culture and may contain as many as 3000 cells per cmm, mainly lymphocytes

3 *Meningo-encephalomyelitic type* In addition to such purely meningeal symptoms, somnolence, disturbances of deep reflexes, paralysis, and anesthetics have been observed in etiologically established cases. These latter symptoms suggest the presence of encephalomyelitis, for which reason Kreis¹⁰ has justly criticized the designation "choriomeningitis" as being too restrictive in certain cases

Recovery is usually complete although sequelae probably related to disturbances in the cerebrospinal fluid drainage have been noted in certain cases. Barker and Ford's⁵ patient developed persistent symptoms which led to a laminectomy being performed at which time the pial space was found to be obliterated by fibrous tissue. Other cases have shown a tendency for one to several relapses to occur

Pathology No pathological report of an etiologically proven case of choriomeningitis has as yet been made. Viets and Warren²⁰ have recorded the pathological findings in a patient with acute lymphocytic meningitis who died with convulsions on the fourteenth day of illness in 1934. The etiology in this case was not determined, the choroid plexus was not examined, and the pathological changes reported for the brain were at variance with those usually observed in experimentally inoculated monkeys. We, therefore, do not feel justified in presenting this case as one of probable choriomeningitis infection

The case reported by Machella, Weinberger, and Lippincott in 1939²¹ was, however, clinically suggestive of this ailment and the pathological findings were similar to those observed in experimentally inoculated monkeys. In this case the meninges were infiltrated with lymphocytes and macrophages and were markedly thickened due to connective tissue multiplication with obliteration of the subarachnoid space. The brain substance was in the main not affected. The ventricles were distended, denuded of their ependyma, and there was a narrow

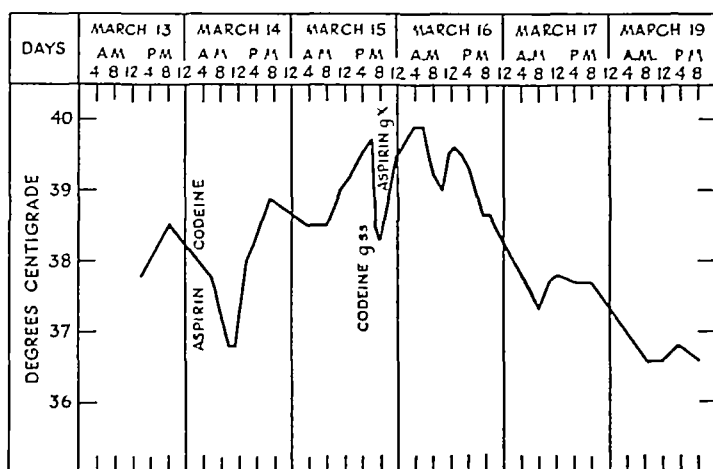


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although chickens, young chicks, canaries, and pigeons have been tried. These negative results in chickens are of interest in view of the successful cultivation of the virus in the tissue of the developing hen's egg by Bengtson and Wooley²⁵. The tissues of the inoculated embryo are rich in virus and many embryos die about the ninth to tenth day, although some of the eggs bring forth living chicks. Such chicks appear rather less active and rather somnolent but usually soon become normal. Laigret and Durand²⁶ reported the finding of the virus in an uninoculated chick embryo, an extremely interesting result if confirmed.

Personally observed cases During a period of 17 months five* cases of choriomeningitis were identified in or near the District of Columbia,^{7, 27, 28} and one at Lancaster, Pennsylvania.²⁷

In five of these cases the virus was recovered from the spinal fluid and in one case where spinal fluid was unattainable the identity of the ailment was confirmed by establishing the absence of specific antibodies early in the disease and their presence subsequent to recovery.

In these six cases, as has been the rule with all reported cases, there was no evidence of contact infection.

This absence of any suggestion of communicability of the disease from person to person raises the question as to the source of the infection.

Virus in mice from infected homes The knowledge that spontaneous infection with choriomeningitis virus had been detected in mice, monkeys, and dogs naturally suggested the existence of an animal reservoir for the virus from which man becomes infected. With a view to testing this hypothesis the homes of these six patients were investigated as to the presence of vermin, mice, rats, and pets.

Gray mice (*Mus musculus musculus*) were trapped in each home and the virus of choriomeningitis was recovered from a pooled emulsion of livers and spleens of mice captured in five of the six homes.

The one failure occurred in connection with the case of a taxicab driver who lived in a poor, isolated abode in nearby Maryland. The patient stated that the home had been overrun with mice and that he had trapped twelve of them from the pantry shortly prior to his illness and that he had also set poison. There was abundant evidence of previous mouse infestation and extensive trapping was undertaken, but only two mice were caught and both proved negative for virus. Thus, while ex-

* Exclusive of two laboratory infections observed during the same period.

posure to mice was established for this patient, we were not able to prove that the mice from the home were actually carrying the virus of choriomeningitis

One home where infected mice were trapped also kept a dog which was examined but no virus was isolated from its liver or spleen

Virus studies on mice from seventy-eight homes More than 400 mice were trapped in homes from various parts of Washington, of which 369 mice survived examination. Of this number 307 were etherized and one kidney and a portion of liver and spleen from each mouse was emulsified in buffered saline (pH 7.6) and 0.03 cc. of the emulsion was inoculated intracerebrally into each of four white mice. When illness resulted, the symptoms and time of death were recorded and a representative sample of forty-six brains from ill white mice were submitted to Surgeon R. D. Lillie, who reported the pathological lesions of choriomeningitis as present in forty-four of them. In two instances the lesions of secondary infection were present.

The final diagnosis of choriomeningitis infection was made, however, by the intracerebral inoculation of four normal mice and of four mice which had been previously immunized to our original strain of choriomeningitis virus.

The inoculation dose of virus employed was 0.03 cc. of a 1:500 suspension of the suspected mouse brain, and in every instance where choriomeningitis virus was finally considered to have been recovered from gray mice, the controls died, while two or more of the immune mice survived. Judged by these criteria choriomeningitis virus was recovered from 65 of a total of 307 gray mice, or approximately one out of every five mice examined was a carrier of the virus. The mice examined were from 78 different homes of which 35 harbored infected mice. Thus it appears that 45 per cent of the mouse infested homes studied were harboring mice infected with choriomeningitis virus. From these 35 infected homes a total of 123 mice were examined of which 65, or 52.8 per cent were carriers of active virus.

The method employed in the above-mentioned studies might be criticized in that white mice were employed as an indicator of infection, since stocks of white mice have on several occasions been found to be spontaneously infected with choriomeningitis virus and it is conceivable that our results were due to the presence of the infection in our white mice rather than in the gray mice which we had trapped.

We feel that this criticism is not valid for the following reasons

1 The same stock of mice were employed in other virus studies but in no instance was choriomeningitis encountered

2 It was noteworthy that mice trapped from certain homes were repeatedly found infected while from other households they were consistently negative, a situation which scarcely would have prevailed had we been dealing with a random infection of our stock mice

3 Gray mice in a number of instances were found to present lesions such as a pleural exudate, fatty liver, and enlarged spleen, which enabled us to predict and later to verify the presence of the virus

Immunity among trapped gray mice In order to eliminate all criticism of the employment of white mice as an indicator of the presence of virus, a further test was undertaken. This study was aimed at determining the immunity of gray mice to choriomeningitis, a procedure in which white mice were not employed. Sixty-two gray mice were, therefore, trapped from 22 homes where infected mice had been previously found. These mice were inoculated intracerebrally with 10 to 15 MLD of our original strain of choriomeningitis virus. Of these 62 mice, 41 survived while 21 died, indicating immunity in 66 per cent.

As a control to this group, 47 gray mice trapped in abodes where only non-infected mice had been found, were similarly inoculated, of which only 5, or 10.6 per cent, survived, while 12 white mice employed as additional controls, all died.

The 22 homes from which mice harboring choriomeningitis virus had been trapped and which supplied the 62 mice employed in this immunity test, had supplied 83 mice which were tested for virus, of which 37, or 47 per cent, were found to be carriers. The two methods, therefore, give confirmatory results. The somewhat higher incidence of immunity as compared to active infection (66.47) is what might be expected and suggests that a portion of the mice had probably freed themselves of readily detectable virus but retained their immunity.

Significance of choriomeningitis in mice The six cases of choriomeningitis in man were widely separated, one in Lancaster, Pennsylvania, two in North West Washington, one in South East, and one in and one adjoining North East Washington. There was no history of contact between any of the cases. Five of the six cases were from homes harboring infected gray mice.

Now if we recall that of 78 homes harboring mice there were 35

which harbored choriomeningitis-infected mice and supplied 5 human cases, while 43 homes harboring non-infected mice supplied only 1 human case, it would appear that these findings are statistically significant, especially when we add to the latter group the large but undetermined proportion of homes which harbored no mice at all and which had no recognized cases of choriomeningitis

Are mice infected from people or people from mice? There is no recorded instance in which one case had contracted choriomeningitis from another, but on the other hand, a number of cases of the disease have developed among laboratory personnel handling infected mice. The wider extent of the infection in mice, as compared to its recognized human prevalence in the District of Columbia, also suggests that mice, not men, are the reservoir for the infection. The patient noted by Findlay, Alcock, and Stern,⁹ who developed choriomeningitis shortly after he had cleaned a shed overrun by mice points in the same direction. Moreover, the tendency for protective antibodies to be relatively most prevalent in the lower economic stratum of society, as noted by Wooley and Armstrong, is hard to explain upon a person-to-person concept of spread, but would be the expected, were mice the source of the infection.

Moreover, the monthly distribution of cases (Table I and Fig. 2) is not inconsistent with this conception. For instance, the Fall peak of cases may be due to the closing of the homes with both mice and men seeking warmer quarters therein. The Spring peak on the other hand may possibly be related to the birth of litters of infected young during the Spring breeding season.

Choriomeningitis virus in mice. Mice are not readily infected with choriomeningitis through feeding of the virus or by exposure to experimentally inoculated cage mates. It would, therefore, appear improbable that five out of the six cases of choriomeningitis should have in every instance infected the mice in their respective homes especially since in each instance the patient was removed to the hospital during the first days of the illness.

On the other hand, Traub¹⁰ also Hiss¹¹ have shown that the virus passes readily from the infected mother to her *in utero* young and that such congenitally infected mice survive birth and may carry the virus for months while mice infected after birth tend to free themselves rapidly of the virus.

Moreover while it has been shown that experimentally inoculated

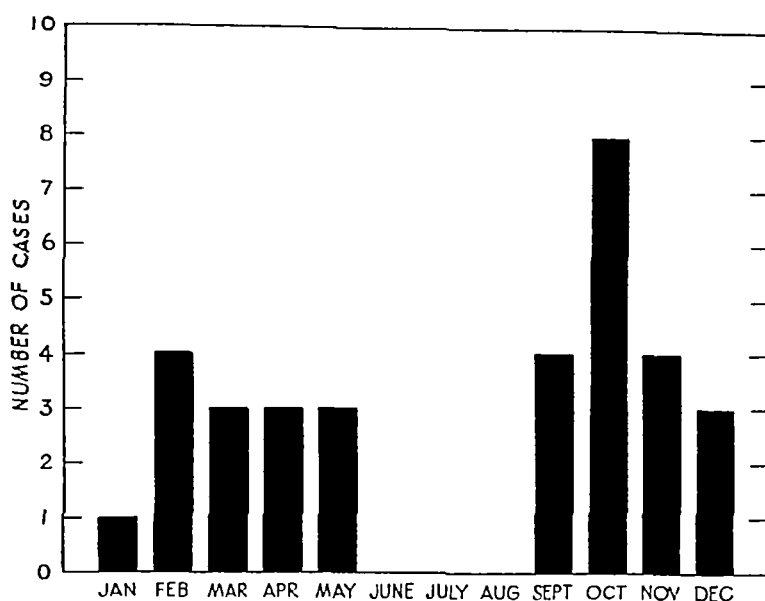


Fig 2—Monthly distribution of cases of choriomeningitis virus infection

mice convey the infection to only a portion of their normal cage-mates even after an exposure of one to two months (Kreis,¹⁰ Haas³⁰), Haas has, however, shown that congenitally infected mice are much more effective conveyors of infection and may transmit the infection to cage-mates after an exposure as short as one hour

Moreover, the finding of 52 per cent of the mice trapped in homes harboring infected mice to be active carriers of the virus, in a study extending over several months, points to a persistent type of infection such as follows the congenital method of spread rather than toward an infection of mice from man

Method of spread of infection between mice and man The presence of the virus in the blood stream and the ready transmission of the systemic type of the infection by subcutaneous inoculations suggest the possibility of an insect transmission

We have, moreover, succeeded in two instances out of several trials in transferring the infection by means of approximately 100 lice taken from an infected monkey and directly transferred to a normal one

Attempts to transfer the infection by bedbugs, rat and mice fleas, and a bloodsucking mite have, however, uniformly failed The virus could be detected in each species when the engorged arthropods were

emulsified and inoculated into normal mice within one hour of the infective feeding, but not after longer intervals. Attempts to convey the infection through biting were entirely negative.

Coggeshall³¹ reported the transmission of choriomeningitis to one guinea pig through the bites of seven *Aedes aegypti* mosquitoes made five days after feeding upon an infected guinea pig. Shaughnessy and Milzer³² succeeded also in infecting Rocky Mountain wood ticks by feeding them on infected animals and demonstrated that the infection could pass through the complete life cycle of the host. Controlled biting experiments were entirely negative but, when infected nymphs were put in the cage with normal guinea pigs, infection occurred. It is probable that these observations have little if any bearing upon the spread of choriomeningitis in nature, for established cases have been noted throughout the winter in latitudes where mosquitoes and ticks are scarce or absent during this period, while in June, July and August, the months when mosquitoes and ticks are prevalent in the northern hemisphere, there have been no proven cases reported (Fig. 2).

The seasonal distribution of cases and the respiratory symptoms so commonly noted in choriomeningitis infections, moreover, suggest a respiratory route of infection. The case of a laboratory worker reported by Lepine, who developed symptoms six days after splashing infectious material into her eye is, moreover, consistent with this route of infection as is the patient reported by Findlay⁹ who developed the disease after cleaning a mouse infested shed.

The virus escapes from infected mice by way of the nasal secretions, urine, and feces, and it is conceivable that dust plays a part in the transfer of the infection to man, although it is possible that contaminated food may play a part, it appears, however, that experimental animals are more susceptible to freshly isolated strains given intranasally than they are by feeding. The investigations of Shaughnessy and Zichis³³ on guinea pigs suggest the possibility that the virus may also be able to pass through the unbroken skin.

Why are there not more human cases? In view of the extent of the mouse infestation and infection in the District of Columbia it is natural to enquire why more human cases of choriomeningitis have not become apparent. As stated above the recognition of the disease has been practically confined to the central nervous system types of the ailment while the systemic type of the infection has probably escaped identification.

The fact that approximately 11 per cent of 2000 sera collected at random possessed neutralizing antibodies for choriomeningitis virus, while the donors largely deny a history of central nervous system disease at any time, points toward an unrecognized infection with the virus as being quite common.

It, therefore, seems probable that choriomeningitis virus infection is more common than is indicated by the occasionally occurring meningeal type of the infection. The reason more cases of this latter type do not occur is probably attributable to the efficient barrier which tends to protect the central nervous system against various infections.

Special considerations The wide range of species susceptible to experimental infection with choriomeningitis along with the finding of naturally infected mice, monkeys, and dogs gives the virus an especial importance for those engaged in animal experimentation with other viruses. For instance, Dalldorf and Douglass³⁴ recovered choriomeningitis virus from four different dog spleens and found suggestive evidence of its presence in several others. Needless to state, the unexpected intrusion of this virus led to some temporary confusion in their canine distemper investigations.

A commercial manufacturer, likewise, has encountered choriomeningitis in the preparation of canine distemper tissue vaccine and Mol-laret³⁵ has raised the question as to whether this virus may not have been responsible for some of the meningeal reactions observed in the early attempts to vaccinate against yellow fever by means of mouse tissue vaccine.

Diagnosis Choriomeningitis should be considered whenever a lymphocytic type of meningitis of unknown etiology is encountered, whether or not it be associated with symptoms of encephalitis and encephalomyelitis. The case reported by MacCallum and Findlay¹⁰ further shows that choriomeningitis may occasionally simulate poliomyelitis. These authors isolated choriomeningitis virus from the spinal fluid as well as repeatedly from the nasal secretions of this case. Furthermore, this infection must be considered in cases of sporadic "grippe-like" infections.

There are at present, however, no characteristic symptoms by which the clinician can with certainty diagnose this infection, although, the finding of a clear spinal fluid with a cell count above 1200, mainly lymphocytes, points, as Baird and Rivers³⁶ have stated and as our experience indicates, toward lymphocytic choriomeningitis. The diagnosis rests ul-

timately, however, upon either the isolation of the virus or the demonstration of a developing immunity

The virus is most readily recovered from spinal fluid or blood drawn preferably at or prior to the height of the attack, and less regularly in later drawn samples. The virus has also been occasionally isolated from the patient's urine and nasal discharges. The inoculation of susceptible animals should be promptly carried out, or when delay is unavoidable the material should be promptly chilled and held near freezing.

A study of the serum for neutralizing or complement-fixing antibodies may also yield diagnostic evidence. Blood for such tests should be drawn with sterile precautions and handled without the addition of anti-coagulants or preservatives of any kind. This statement is prompted by the fact that we receive at the National Institute of Health many samples mailed from various parts of the United States which contain anti-coagulants, glycerine, or other preservatives. It is also surprising how frequently blood is mailed in cotton stoppered containers from which the serum, of course, uniformly escapes.

Virus-neutralizing antibodies are usually not demonstrable in the blood before 6 to 10 weeks following the onset of symptoms, but in our experience, they invariably appear in established cases. Howard,³⁷ however, reported two cases in which demonstrable virus-neutralizing antibodies failed to appear following the attack. Once established, neutralizing antibodies tend to persist for months or even years. Baird and Rivers³⁸ report the case of a child 8 years of age in which the antibodies disappeared after 8 months. We have, however, examined patients as much as 3½ years after the attack and found the antibodies undiminished.

It is desirable that blood be drawn early in suspected cases and again some 6 to 10 weeks following the attack. Both samples should then be tested for antibodies when a definite increase in the later drawn as compared to the earlier drawn specimen may be considered of diagnostic significance.

Complement fixation, as carried out by Lepine, Mollaret and Sutter³⁹ and by Smadel, Burd and Wall⁴⁰ is also a valuable diagnostic procedure. Complement fixing antibodies make their appearance earlier and tend to be less persistent than the slower developing neutralizing antibodies.

Treatment There is no specific treatment of proven value known. The favorable experimental results secured in mice with prontosil by

Rosenthal, Wooley and Bauer⁴⁰ have not been consistent and when effective were apparently dependent upon early administration and more nearly approach prophylaxis than they do treatment

Leichenger, Milzer and Lack⁴¹ feel that sulfanilamide was effective in one patient observed by them in spite of the fact that the patient suffered four distinct relapses and the illness persisted for 4 months

Spinal drainage is the one measure that frequently has afforded relief from the severe headache and vomiting. Cellular changes in the spinal fluid may persist for a considerable period following the disappearance of acute symptoms and accumulating instances where one or more relapses occur indicate that there is danger in discharging the patient to full activity before the spinal fluid has returned to normal

Prevention There are many details of the exact manner of spread for the virus yet to be determined, the findings reported do, however, suggest that prevention would be served by the construction of homes with a view to rendering them mouse proof and by reducing or eliminating mouse infestation from quarters frequented by people

POLIOMYELITIS

Poliomyelitis is a disease that has been much studied but the investigations have, to date, singularly failed to answer definitely many fundamental epidemiological considerations relating to this disease, such as the method of spread of the virus, and the portal of its entry to the central nervous system. A noteworthy recently established fact is that the virus of poliomyelitis may exist in the intestinal tract of man from which it escapes, in readily detectable amounts, along with the dejecta. The significance of this fact is, however, a matter of controversy and any attempt to present the *pros* and *cons* of this discussion would be time-consuming and without hope of reaching a definite or convincing conclusion at this time. I shall, therefore, forego consideration of the controversy raised by this recent development and proceed to a consideration of the cotton rat and white mouse in poliomyelitis research

In so far as availability, cost and such general considerations are concerned the cotton rat and white mouse are admirable laboratory animals. Their suitability for poliomyelitis research is, however, dependent upon the degree and uniformity of susceptibility, the incubation period, and the definiteness of the symptoms. It is these factors which I wish to consider

Susceptibility to new strains The susceptibility of the cotton rats to new strains is apparently low, for instance, in 1937 and again in 1938 we were able to transmit a monkey-adapted strain of poliomyelitis from Lansing, Michigan, to one of two and one of eleven cotton rats, respectively, after an incubation period of 29 days in each instance, but attempts at further passage failed. In 1939 one of four inoculated rats developed symptoms and from this rodent the strain has been successfully carried through fifty-five successive transfers and after seven generations was successfully conveyed to white mice.

During 1939 we had one of four cotton rats develop symptoms following inoculation with a strain of virus from Niagara Falls after an incubation period of 41 days. We also produced symptoms in one of several rodents with a strain of virus from Detroit and succeeded in carrying it through three generations. Further attempts at transfer failed in both instances, as did attempts to convey six additional strains to cotton rats.

Other investigators have attempted to convey many strains of poliomyelitis to cotton rats but with few successes. For instance, Jungeblut and Sanders⁴² succeeded, three times, in passing a virus to cotton rats, employing the monkey-adapted S K poliomyelitis strain, which was originally of fecal origin. After passage in cotton rats the virus was found to be pathogenic for white mice, in which species it showed extreme potency and a remarkable capacity to pass the central nervous system barrier, but with mouse passage it tended to lose its pathogenicity for monkeys. This virus differs markedly from the mouse-adapted Lansing strain of virus, which was of nervous system origin, and it is conceivable that neuro and fecal strains may behave differently. The authors kindly supplied me with their strain of virus and I regret that I have not been able to work with it, due to the stress of more urgent but not necessarily more important duties. Therefore, I am not able to express an authoritative opinion on the authors' contention that their murine virus is immunologically one of poliomyelitis. The most convincing evidence set forth by the authors in support of this contention is perhaps, the fact that the pseudoglobulin concentrate from an R M V antipoliomyelitis horse serum "neutralized" their murine virus in high concentrations. It is noted, however, that an R M V antipoliomyelitis serum from a convalescent monkey gave no neutralization against the same strain of virus. The authors explain this discrepancy in behavior of the two anti-R M V

sera as due to "The enormous potency of the hyperimmune horse serum breaking down immunological strain differences" The authors, however, also mention in passing that diphtheria antitoxin (pseudoglobulin) in several tests also inactivated large doses of murine virus

It is difficult to harmonize these results on the basis of specific neutralization and I am wondering if the authors have considered the possibility that their concentrated sera may have contained a preservative I make this inquiry because a preservative is required, by Federal regulation, to be added to serum concentrates if prepared for human use and intended for inter-State sale Moreover, many producers follow Federal requirements in preparing sera for intra-State use The presence of a preservative such as merthiolate or phenol, acting for $1\frac{1}{2}$ hours at 37° C and over night in the ice box prior to inoculation, would have opportunity to destroy a portion of the virus, the result would simulate a true neutralization and supply a ready explanation for the odd results secured by the authors Should this possible explanation be the correct one, the remaining evidence of immunological relationship with poliomyelitis would be so slight as to cause one to doubt whether the murine virus was related to poliomyelitis virus at all

A personal communication has recently been received from another investigator who claims to have transferred the P M V strain of poliomyelitis to cotton rats He kindly sent me some of this virus strain and when inoculated into cotton rats it produced symptoms similar to those caused by the Lansing strain, but it has not been further identified at the National Institute of Health

The evidence thus indicates that the cotton rat is a far less satisfactory animal for the primary isolation of poliomyelitis strains than is the monkey

Susceptibility to Lansing strain Cotton rats and white mice appear to be quite susceptible to the adapted Lansing strain The incubation period in the former is usually 3 to 8 days, while in white mice symptoms become apparent usually in 2 to 10 days following inoculation, but the interval has been observed to be as short as 24 hours and as long as 93 days In both these rodent species the symptoms are very distinct, paralysis of one or more legs being usually first observed, while paralysis of the neck, back, and tongue have been seen Death occasioned by respiratory paralysis usually takes place within 12 to 48 hours of the first recognized symptoms White mice almost uniformly succumb when 03 cc

of a suspension of infected mouse brain in a dilution up to 1:500 is employed and a portion of the inoculated mice will develop symptoms with dilutions as high as 1:10,000. Occasionally an animal recovers after having developed symptoms. In such instances of recovery muscle atrophy and deformities usually develop.

Route of inoculation. The only successful route of inoculation for rodents employing the Lansing strain of virus consists in the direct inoculation of the central nervous system. Intranasal, intraocular, subcutaneous, intraperitoneal inoculations, as well as feeding, have all failed to induce infection. Unless these negative results can be overcome it is difficult to see how these rodents can contribute much toward elucidating the natural route of infection or transit of the virus in man.

Immunity. Mice and cotton rats which have recovered from paralytic attacks induced by the Lansing strain are solidly immune to intracerebral inoculation with the virus.

Humoral immunity. When Lansing virus-infected mouse brains are inoculated under the skin of mice or cotton rats they develop potent humoral antibodies readily demonstrable by the serum-virus protection test in mice or cotton rats. Such antibodies exert a slight protective action against intracerebrally inoculated minimal infective doses of virus (Table II). It is conceivable, however, that the protective action may be due to the artificial method of inoculation since the needle in some instances probably produces some bleeding at the inoculation, where the plasma coming into direct contact with the virus would, if immune, tend to prevent infection. The artificial method of inoculation necessary to bring about infection in mice, therefore, tends to cast doubt upon the significance of the degree of protection afforded subcutaneously immunized mice when minimal infective doses of virus are employed.

Humoral immunity in the population. Approximately 300 human sera from various sources have to date been submitted to the serum-virus neutralization test in white mice, employing the mouse-adapted Lansing strain of virus. The test is rapid, requires but .45 cc. of serum, and the results are usually definite, easily read, and readily repeatable (Table III).

This group of 300 tested human sera is larger than any series yet reported by a single laboratory employing monkeys; however, we consider that we have just begun. No detailed analysis of our results will, therefore, be attempted at this time. In general the results secured to

Chemotherapeutic studies Cotton rats and white mice along with the Lansing strain of virus are also being utilized in the search for curative agents in poliomyelitis and they will permit studies to an extent practically impossible with the monkey

Is the Lansing strain exceptional or peculiar? In view of the various studies now being pursued with the Lansing strain of virus it seems appropriate to inquire if this strain of virus is exceptional or peculiar. The virus originated from what was clinically considered to be a typical case of fatal bulbar poliomyelitis. The clinical and pathological picture produced in monkeys with this strain of virus both before and after its transmission to cotton rats and white mice is identical and confirms the opinion that the Lansing strain is one of typical poliomyelitis. The finding of virus-neutralizing antibodies in 71.5 per cent of approximately 300 human sera from various localities of the United States further indicates that the Lansing strain of virus is immunologically a commonly occurring one. The finding that four out of seven antisera collected from monkeys convalescent from various strains of poliomyelitis protected mice against the Lansing strain of poliomyelitis virus points in the same direction.

The sera tested which gave positive results were as follows

	<i>Results</i>
1 From Lennette (P M V)	+
2 From Niagara Falls, 1938	+
*3 From S D Kramer, Michigan (Rhesus 91)	+
*4 From S D Kramer, Michigan (Rhesus 83)	+
5 From Aycock, Boston	—
6 From Charleston, S C, 1939	—
†7 From S D Kramer, Michigan (Rhesus 41)	—

The failure of three convalescent monkey sera to show protection against the Lansing strain appears to be in agreement with strain difference indicated by the work of Burnet and Macnamara,⁴³ Weyer,⁴⁴ Paul and Trask,⁴⁵ Kessel and co-workers,⁴⁶ and others. This apparent confirmation, however, rests on an assumption since we have not demonstrated that the three sera, which lacked apparent neutralizing antibodies for the Lansing strain, actually possessed antibodies at all, since the homologous viruses had not been adapted to mice and we did not feel justified in sacrificing monkeys for the purpose.

* A communication from S D Kramer subsequent to delivery of this paper reveals that sera 3 and 4 were from monkeys immunized against the Lansing strain of virus.
 † Animal number 7 died of tuberculosis.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 2—*The New York Academy of Medicine Annual Meeting* Executive session—a) Reading of the Minutes, b) Presentation of certificates of Fellowship ¶Presentation of annual reports (by title only), The council, the trustees, the treasurer committees ¶Presidential address "What is The New York Academy of Medicine?" Malcolm Goodridge ¶Scientific program Newer knowledge of the steroid hormones—
 1) Chemical, physiological and clinical aspects of the estrogens, Ephraim Shorr, Assistant Professor of Medicine, Cornell University Medical College, b) Chemical, physiological and clinical aspects of the androgens, John Eager Howard, Associate in Medicine, Johns Hopkins University, School of Medicine, c) Chemical, physiological and clinical aspects of progesterone, William M Allen, Professor of Obstetrics and Gynecology, Washington University, School of Medicine ¶Report on election of trustee and fellows

JANUARY 16—*The Harvey Society in affiliation with The New York Academy of Medicine* The fourth Harvey lecture, "Adjustment of Nerve Endings," Dr Carl C Speidel, Professor of Anatomy, University of Virginia

SECTION MEETINGS

JANUARY 3—*Surgery* Reading of the minutes ¶Presentation of cases—a) *Staphylococcus aureus* septicemia, osteo-

myelitis of femur and humerus, suppurative pericarditis Recovery, Francis McG Donehue, Discussion, Hugh Chaplin, b) *Staphylococcus aureus* septicemia, osteomyelitis of ilium, suppurative pericarditis Recovery, A J Abeloff Discussion, Frank L Meleney, c) Osteomyelitis of femur, humerus and ilium, retroperitoneal abscess Recovery, Frank B Berry ¶Papers of the evening, a) The use of sulfanilamide locally in peritoneal infections, James E Thompson, Discussion, R S Mueller (by invitation), b) Modern treatment of war wounds, Charles Bove (by invitation), Discussion, John A McCreery ¶General discussion

JANUARY 7—*Dermatology and Syphilology* Presentation of cases—a) Vanderbilt Clinic, b) Miscellaneous cases ¶Discussion of cases ¶Executive session

JANUARY 7—*Combined Meeting The New York Neurological Society and the Section of Neurology and Psychiatry* Reading of the minutes ¶Papers of the evening—a) Neuropsychiatric disturbances in Addison's disease, George L Engel (by invitation), Sidney G Margoline (by invitation), Discussion, Israel Wechsler, Norman Jolliffe (by invitation), b) The narcoleptic-cataplectic syndrome. An excessive and dissociated reaction of the sleep-regulatory mechanism, and its accompanying mental states, Samuel Brock, Benjamin Wiesel (by invitation), c) Oliver Wendell Holmes—A Precursor of Freud, C P Oberndorf, Discussion, Tracy I Putnam, John Alfred Parsons Millett (by

invitation), Foster Kennedy "General discussion" "Executive session"

JANUARY 8—*Combined Meeting Section of Historical and Cultural Medicine and the New York Physical Therapy Society* Executive session—a] Reading of the minutes, b] Appointment of nominating committee. "Papers of the evening— a] August Kekule, first of the modern chemists, Herman Goodman Discussion, Victor Robinson (by invitation), Chester Myers, b] Celebrated figures in electrotherapy, Richard Kovacs, Discussion, Madge C I McGuinness, Iago Galdston

JANUARY 9—*Pediatrics* Reading of the minutes "Papers of the evening— a] Deafness in little children Early detection, management and treatment Demonstration by children of the New York League for the Hard of Hearing, Edmund Prince Fowler, Discussion, J Taylor Howell, b] Virus diseases of the eye in infancy, Gordon M Bruce Discussion, M Sanders (by invitation) c] Newer conceptions of ophthalmia neonatorum, J Vincent Flack (by invitation), Discussion Eleanor I Adler (by invitation)

JANUARY 15—*Genito - Urinary Surgery* Reading of the minutes "Papers of the evening. *Commemorating the Twentieth Anniversary of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital* a] The adequate treatment of prostatic disease with special reference to pathology, Roy B Henline b] Management of carcinoma of renal pelvis with report of an interesting case, Thomas J Kirwin c] The role of the Brady Foundation in urology at the New York Hospital Oswald S Lowesley d] Reminiscences of early experiences in urology in New York City, Colin I Begg "General discussion" "Executive session"

JANUARY 15 *Otolaryngology* Reading of the minutes "Presentation of cases"

a] *Pneumococcus Type III—mastoiditis and meningitis, operation, recovery*, Alvin M Street (by invitation), b] *Frontal sinusitis, osteomyelitis and meningitis, operation, recovery*, J Swift Hanley, c] *Meningitis, labyrinthitis, operation, recovery*, Jackson A Seward, d] *1 Total laryngectomy, 2 Foreign body in maxillary sinus*, Eugene Mowle, e] *Specimen of healed petrositis*, J Winston Fowlkes "Paper of the evening, *Cancer of the paranasal sinuses*, William L Watson, Discussion, Douglas Quick "General discussion"

JANUARY 20—*Ophthalmology* Exhibits 7.00 to 8.30 o'clock (by invitation), a] A device for doing light threshold studies, Jacob B Feldman, Philadelphia b] A demonstration of some effects of aniseikonia, Hermann M Burian, Hanover, New Hampshire, c] The central visual field (angioscotometry), John M Evans, George Graham, Charles Rosenthal d] Comparative micranatomy of the interior chamber angle in mammalia, Manuel Uribe Troncoso e] Demonstration of contact glass technique "Reading of the minutes" "Papers of the evening Clinical Evaluation of Recent Advances in Examination and Functional Testing of the Eyes— a] Orthoptics, Maynard C Wheeler, b] Gonioscopy, John M McLean Baltimore (by invitation) Discussion, Manuel Uribe Troncoso (by invitation) c] Aniseikonia, Hermann M Burian, Hanover, New Hampshire (by invitation), d] Light threshold studies Jacob B Feldman Philadelphia (by invitation) e] Angioscotometry, John M Evans (by invitation)

JANUARY 21 *Medicine* Reading of the minutes "Papers of the evening— a] Avitaminosis from the point of view of internal medicine Thomas T Macle b] Avitaminosis from the point of view of neurology and psychiatry Norman Tollife Discussion William C MacTavish Gilbert Dilldorf "General discussion" "Executive session"

JANUARY—Orthopedic Surgery There was no meeting of the Section of Orthopedic Surgery in January because of the annual meeting of the American Academy of Orthopaedic Surgeons in New Orleans, January 12-16

JANUARY 28—Obstetrics and Gynecology
 Reading of the minutes ¶ Papers of the evening (*Program by Sloan Hospital for Women*) "Difficult Labors"—a] Introduction, B P Watson, b] Prognosis of labor in the prenatal patient, J W Draper (by invitation), c] Problems of first stage, W E Caldwell, d] Difficulties due to occiput-posterior position, D A D'Esopo (by invitation), e] The android pelvis as a cause of difficulty, H C Moloy (by invitation), f] The lessons infant autopsies teach us regarding breech delivery, J C Boyd (by invitation), g] Trial labor—what is it? B P Watson

AFFILIATED SOCIETIES

JANUARY 20—New York Roentgen Society in affiliation with *The New York Academy of Medicine* Symposium on Radiation in Operable Breast Cancer, Douglas Quick ¶ Discussion, Edith Quimby (by invitation), Frank E Adair, William Harris, Alfred F Hocker (by invitation), Milton Friedman ¶ Executive session

JANUARY 23—New York Pathological Society in affiliation with *The New York Academy of Medicine* Papers of the evening—a] The morphogenesis and significance of "intercapillary glomerulosclerosis" (15 minutes), Arthur C. Allen (by invitation), Mount Sinai Hospital, b] Morphological analysis of tuberculous lesions in adults (40 minutes), Kornel Terplan (by invitation), Buffalo General Hospital, discussion was opened by J Burns Amberson and Eugene L. Opie. ¶ Executive session

DEATHS OF FELLOWS

BEGG, COLIN LUKE 118 East 54 Street, New York City, born in Glasgow, Scotland, December 9, 1873, died in New York City, January 15, 1941, received the degree of A.B. from Queen's University, Canada, in 1895 and graduated in medicine from the University of Toronto in 1899, elected a Fellow of the Academy May 24, 1906

Dr Begg served as professor of urology at the New York Post-Graduate School of Medicine and Hospital and was consulting urologist to the New York Skin and Cancer Hospital, surgeon to the New York Hospital Out-Patient Department, and a member of the staff of the Department of Urology, the

James B Brady Foundation at that hospital

Dr Begg was a diplomate of the American Board of Urology and one of its founders, a Fellow of the American Medical Association, a member of the American Neisserian Medical Society and the County and State Medical Societies

DAVIS, ACHILLES EDWARD 40 East 61 Street, New York City, born in Harrodsburg, Kentucky, February 18, 1866, died in Scarsdale, New York, January 17, 1941, received the degree of B.A. in 1886 and M.A. in 1889 from the Central University of Kentucky, graduated in medicine from the University of Louisville in 1889, elected a Fellow of the Academy February 2, 1899

Dr Davis was consultant on diseases of the eye to the New York Post-Graduate Medical School and Hospital, and consulting ophthalmic surgeon to the Manhattan State

Hospital at Central Islip, Long Island, since 1889, the United Hospital at Port Chester, New York, since 1911, and the Ossining Hospital at Ossining, New York, since 1913. He was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the Pacific Coast Oto Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, the Association for Research in Ophthalmology, Inc, and the County and State Medical Societies.

Especially known for his work in cataract cases, Dr Davis wrote many papers on that and allied subjects. Among his publications were "The Refraction of the Eye," 1900, "Handbook of the Anatomy and the Diseases of the Eye and Ear," (in collaboration) 1904, "Eye, Ear, Nose and Throat Nursing," (in collaboration) 1905, and "Medical Treatment of Cataract," 1937. He also wrote the section on refraction in the "American Encyclopedia of Ophthalmology," 1919.

Dr Davis was a member of the Officers' Reserve Corps and served as Captain in the United States Army Medical Corps during the World War.

ESTES, WILLIAM LAWRENCE, Sr. Bethlehem, Pennsylvania, born in Brownsville, Tennessee, November 28, 1855, died in Bethlehem, Pennsylvania, October 20, 1940, graduated in medicine from the University of Virginia in 1877 and from University Medical College of New York in 1878, received the honorary degree of M.A. from Bethel College, Kentucky, in 1893, elected a Fellow of the Academy December 6, 1906.

Dr Estes was emeritus surgeon-in-chief of the St. Luke's Hospital, Bethlehem, lecturer on physiology and hygiene at the Lehigh University, 1883-1923, and chief surgeon to the Lehigh Valley Railroad, 1888-1904. He was a Fellow of the International Surgical Association, the American Surgical Association, the American College of Surgeons, an Associate Fellow of the College of Physicians, an Honorary Member of the Association of Industrial Surgeons of America, a member of the Pennsylvania State Medical Society and the American Medical Association.

NEAL, PHILEMON HAWKINS 145 East 74th Street, New York City, born in South Boston, Virginia, October 21, 1896, died in New York City, January 21, 1941, graduated in medicine from the Medical College of Virginia in 1923, elected a Fellow of the Academy April 5, 1934.

Dr Neal was assistant surgeon to the New York Eye and Ear Infirmary. He was a Fellow of the American College of Surgeons and the American Medical Association, a diplomate of the American Board of Otolaryngology, and a member of the American Academy of Ophthalmology and Otolaryngology, and the State and County Medical Societies.

PUTTI, VITTORIO Bologna, Italy, born in Bologna, March 1, 1880, died in Rome, November 1, 1940, graduated in medicine from the University of Bologna, July 1, 1903, elected an Honorary Fellow of the Academy November 18, 1926.

Dr Putti was professor of orthopedic surgery and dean of the School of Medicine at the University of Bologna, and director of the Rizzoli Orthopedic Institute of Bologna. He was noted for his studies on tuberculosis of the bones and was the author of numerous books on orthopedics.

ROBERTSON, VICTOR ARTHUR 51 Lighth Avenue, Brooklyn, N.Y. born in Brooklyn, April 19, 1861, died in Brooklyn, December 22, 1939, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1883, elected a Fellow of the Academy March 1, 1923.

Dr Robertson was consulting surgeon to the Coney Island Hospital, a member of the County and State Medical Societies, a Fellow of the American Medical Association and a Fellow of the American College of Surgeons.

SCHULDER, PAUL FERDINAND 160 East 48 Street, New York City, born in Vienna, Austria, February 15, 1888, died in New York City, December 8, 1940, graduated in medicine from the University of Vienna in 1909, elected a Fellow of the Academy November 5, 1931.

Dr Schuller was a assistant psychiatrist at

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OLIVER WENDELL HOLMES
A PRECURSOR OF FREUD*

C P OBERNDORF

OLIVER WENDELL HOLMES was one of the favored few who are born into a setting of maximum privilege and opportunity. On both sides his parents were connected with the most influential families of that select group of Cambridge and Boston to which he later gave the name of Brahmins. His education was carefully guided into the best channels from the time he entered elementary school until he had completed the envied postgraduation medical studies in Europe under the famous masters of Paris. Holmes was one of the fortunate few who are capable of making the most of the rare advantages offered to them.

In 1871 Holmes, just turning sixty, had reached a position of distinction never attained by any other American physician or perhaps by any physician. In erudite Cambridge, regarded as the fountainhead of American literature and learning, he had become an arbiter whose word of praise sometimes decided the destiny of young authors who flocked to this seat of culture. In this literary center the 'Laughing Doctor,' as Holmes was called, had become something more than an arbiter—a liberal, generous and beloved autocrat.

At this time Holmes also was rounding out a distinguished career as a physician which had included a long service as dean of the faculty of medicine at Harvard. His lectures had become renowned because of his learning, wit, wisdom and progressiveness. Much earlier, in 1843, his fame was already secure. Almost at the outset of his career he made a contribution to science which would have assured him a permanent place among the pioneers of medicine had his life-work ended then, namely, his essay "On the Contagiousness of Puerperal Fever"¹

The demonstration of the contagious nature of puerperal fever is shared by Holmes and Semmelweis of Austria. The latter has been hailed throughout Europe for this revolutionary discovery, although he published his observations four years after Holmes. Holmes was compelled to face strong opposition to the new theory from reactionary New England colleagues but did not have to meet the bitter antagonism and suffering which Semmelweis endured in Vienna. Persecution lent to Semmelweis "the aura of a martyr." On the other hand, in the career of Holmes, the observations concerning puerperal fever assumed the place of an episode in a succession of significant activities. The simple normalcy of the genius of Holmes needed no martyrdom or eccentricity for its emphasis and he affected none.

With the theory of puerperal fever established, Holmes threw himself into the investigation and examination of the great mass of knowledge which physics and chemistry were beginning to deliver into the hand of medicine. To much of this he added clarifying comment, original amplification and the weight of his authority, as in the founding of the Harvard Dental School. It is rarely recalled that, writing to William T. G. Morton on November 21, 1846 concerning the introduction of sulphurous ether, under the name of Letheon, to produce temporary loss of consciousness, he says, "All I will do is to give you a hint or two as to names—or the name to be applied—anesthesia"² Here, as was so often the case with Holmes' apt and pithy expression, the name anesthesia attained universal adoption.

The period in which Holmes (1809-1894) lived and worked saw tremendous change in medical theories and attitudes. Science was zig-zagging forward. But it was also a period when an opposite tendency pervaded New England thought, not sporadically but as a general and sustained movement. The self-frustration and rigid repression long enforced by Calvinistically inclined clergy no longer found a compen-

satory outlet in the physical struggle for the conquest of resistive New England fields and mountainside. As an escape from emotional suppression many an individual and thwarted group in isolated New England villages were turning to mysticism, a serene substitute for an earlier hysterical reaction, "witchcraft," which had a century previously swept the countryside.

The semi-scientific discoveries of Mesmer had reached the American shore and were beginning to be incorporated with mystical ruminations in ingenious ways. Thus, this era of scientific advance supported odd cults, most of which in one way or another weakened the severe ecclesiastical structure and attempted to cure some of the conversion symptoms for which social and incidental repression could be held responsible. Phineas Quimby in bleak Maine and the mystics, Andrew Jackson Davis and Thomas Lake Harris, combining the power of suggestion with the faith of prayer, performed startling cures in New England and New York. At this time, too, Mary Baker Eddy boasted that her poems were printed "side by side with those of Whittier, Holmes and Phoebe Carey and are preserved in the files of the Lynn (Massachusetts) papers."³ She later succeeded in shrewdly merging conflicting tendencies in an illusive paradox under the system she called Christian Science.

Holmes, for all his preferential social background and academic training, could not escape during childhood in his home and in his subsequent contacts the impact of repressive environmental influences. Holmes' father was a Calvinist minister, paradoxically, from all account a rather genial Calvinist, but he firmly believed in predestination and preordination. Holmes attempted to escape from these concepts into science and scholarship, but they also created in him a bitter antipathy and lifelong rebellion against the crippling effects of damnation theology. The drive to counteract and correct such an irremediable philosophy appears time and again in his essays and in his three novels which are critic much to Holmes' annoyance, scoffingly called "mediated novels."

Holmes was first and foremost the physician with his thinking dominated by his medical training and his daily experiences. He was also a theological reformer a philosopher and as we shall see according to our present concept of this specialty a psychiatrist. In this field his theories and approach are those of psychoanalysis and antedated Freud in many striking and important particulars.

Freud is reported to have replied to a Prussian official, who greeted him as the discoverer of the unconscious, with the words "The poets and philosophers before me have discovered the unconscious, I have discovered the scientific method with which the unconscious can be studied"⁴

Holmes cannot be regarded as an inspired poet. His poetry seems to have followed a conventional manner of expression, then popular. It is the philosophic quality of Holmes' mind which led him to the discovery of many postulates which Freud, nearly a quarter of a century later, offered to a ridiculing academic group in Vienna in the very university where Semmelweis met similar discouraging rebuff. Holmes' precocious psychological pronouncements and likewise his unremitting fight for liberality and generosity in the estimation of mental aberration encountered relatively mild opposition in a milieu where the abolitionists had so long been battling for the physical freedom of all men. It is likely that into their zeal for the liberation of the negro, the abolitionists may have displaced and vicariously invested much of the energy unconsciously aimed at self-liberation from their own captivities. Less personal sacrifice was required to fight for the freedom of the distant blacks than to attempt to disturb their own immediate imprisoned selves.

The year 1871 has been mentioned because it was the one in which Holmes delivered before the Phi Beta Kappa Society of Harvard an address entitled, "Mechanism in Thought and Morals." It was carefully revised, expanded and annotated before it was printed in "Pages from an Old Volume of Life."⁵ So far as I can determine it has lain there unnoticed. I find no reference to it in accounts of Holmes' contributions to medicine. However, Van Wyck Brooks in "The Flowering of New England, 1815-1865,"⁶ an absorbing study of that brilliant period of American cultural development, states that the essay of Holmes "was a brilliant anticipation of Dr. Freud." He also writes, "Dr. Holmes, perhaps unwittingly, had played into the hands of Dr. Darwin. He had played into the hands of Dr. Freud, and he had played into the hands of another doctor of whom he had never heard, Dr. Marx."

The cornerstone of Freud's theory is the importance and the influence of unconscious mentation and of repression, a force, as we have seen, not entirely unknown in New England. Freud has insisted upon the distinction between unconscious and subconscious to the extent that it appeared as though the term unconscious were originated by

him * In most of the writings of predecessors and contemporaries the term subconscious had been regularly used to indicate mental operations which occurred below the level of consciousness. Other important pillars in the structure of psychoanalysis are the free association of ideas, the role of the censor, emphasis on the content of dream life and its import as a revelation of unconscious mentation, and in the first work of Breuer and Freud,⁸ the existence of several personalities in the same individual.

Upon all these questions Holmes has much to say in the "Mechanism of Thought and Morals," and says it clearly, forcefully and unequivocally. The object of his thesis is never in doubt, namely, that such a thing as absolute freedom of the will cannot exist because of unconscious processes which are continually affecting the individual's conscious activity. Were it for this reason alone Holmes affirms we must regard many deviations in conduct with charity and understanding. I quote "Do we ever think without knowing that we are thinking? The question may be disguised so as to look a little less paradoxical. Are there any mental processes of which we are unconscious at the time, but which we recognize as having taken place by finding certain results in our minds?"

It is worth while to note that Holmes, without accenting it, uses the word unconscious in the sense which many psychoanalysts, including myself, thought had been originated by Freud. That the concept of the unconscious is not accidental may be proven by an additional citation from Holmes. "Unconscious activity is the rule with the actions most important to life. The lout who lies stretched on the tavern-bench, with just mental activity enough to keep his pipe from going out, is the unconscious tenant of a laboratory where such combinations are being constantly made as never Wohler or Berthelot could put together, where such fabrics are woven, such problems of mechanism solved such a commerce carried on with the elements and forces of the outer universe that the industries of all the factories are mere indolence and awkwardness and unproductiveness compared to the miraculous activities of which his lazy bulk is the unheeding centre."

Holmes not only appreciated the constant and restless activity of the unconscious but also that from the unconscious come those urgent drives which thrust aside the more deliberate thoughts and planning.

those affect-laden urges that lend conviction and power to expressed thought. For example "And so the orator,—I do not mean the poor slave of a manuscript, who takes his thought chilled from its mould, but the impassioned speaker who pours it forth as it flows coruscating from the furnace,—the orator only becomes our master at the moment when he himself is taken possession of, by a sudden rush of fresh inspiration. How well we know the flash of the eye, the thrill of the voice, which are the signature and symbol of nascent thought,—thought just emerging into consciousness, in which condition, as is the case with the chemist's elements, it has a combining force at other times wholly unknown!"⁵

The mechanism of the association of ideas, a postulate of psychoanalysis and the one upon which therapeutic psychoanalysis is fundamentally based, did not escape Holmes. In this connection I shall quote paragraphs scattered throughout the Phi Beta Kappa essay but here gathered into a sequence to give emphasis to the understanding which Holmes possessed of the mechanism of thought-operation and thought-flow.⁵

"We wish to remember something in the course of conversation. No effort of the will can reach it, but we say, 'Wait a minute, and it will come to me', and go on talking. Presently, perhaps some minutes later, the idea we are in search of comes all at once into the mind, delivered like a prepaid bundle, laid at the door of consciousness like a foundling in a basket. How it came there we know not. The mind must have been at work groping and feeling for it in the dark, it cannot have come of itself. Yet, all the while, our consciousness, so far as we are conscious of our consciousness, was busy with other thoughts."

This idea of unconscious associative thought-functioning is expressed more concisely as follows: "The more we examine the mechanism of thought, the more we shall see that the automatic, unconscious action of the mind enters largely into all its processes. Our definite ideas are stepping-stones, how we get from one to the other, we do not know, something carries us, we do not take the step."

But quite in harmony with his philosophy of insisting that society take into account unconscious factors in evaluating human conduct and at the same time holding that this does not exempt the individual from definite, undeniable responsibility for his acts, he adds "The flow of thought is, like breathing, essentially mechanical and necessary, but incidentally capable of being modified to a greater or less extent by con-

scious effort Our natural instincts and tastes have a basis which can no more be reached by the will than the sense of light and darkness, or that of heat and cold ”

To show the scope with which Holmes has covered psychoanalytic mechanisms we find the following excerpts in regard to dreams—the first hints at wish-fulfillment “We not rarely find our personality doubled in our dreams, and do battle with ourselves, unconscious that we are our own antagonists Dr Johnson dreamed that he had a contest of wit with an opponent, and got the worst of it of course, he furnished the wit for both Tartini heard the Devil play a wonderful sonata, and set it down on awaking Who was the Devil but Tartini himself? I remember, in my youth, reading verses in a dream, written as I thought, by a rival fledgling of the Muse They were so far beyond my powers, that I despaired of equalling them, yet I must have made them unconsciously as I read them ”

In a second comment on dreams Holmes indicated that in dream-life problems are solved and that we may unconsciously act in obedience to these solutions in waking life—a theory advanced by one of the early analysts, Alphonse Maeder “The cases are numerous where questions have been answered, or problems solved, in dreams, or during unconscious sleep Two of our most distinguished professors in this institution have had such an experience, as they tell me, and one of them has often assured me that he never dreams Somnambulism and double-consciousness offer another series of illustrations ”

Holmes also goes thoroughly into the question of the quantity and quality of thought-flow—of the ‘internal movement’ of which we are wholly unconscious “when one idea brings up another, of the indestructibility of memories and affects of unconscious factors in plagi-
arism of the function of censorship of co-conscious mentation and double consciousness, the duality of our personalities of the differences in the type of thought in males and females and of the effects of sexual frustration in producing physical symptoms and character traits

All of these concepts are stated in *Mechanism of Thought and Morals* and constitute a scientific formulation and recapitulation of thoughts which Holmes had confirmed during his long career as a practicing and consulting physician As mentioned Holmes is the author of three novels the first of which *Elsie Venner—A Romance of Destiny* appeared in 1850 It was followed in 1867 by a somewhat similar novel

"The Guardian Angel," and in 1884-5 by "A Mortal Antipathy." Although "Elsie Venner" enjoyed something of a popular success, literary critics dealt none too kindly with this or Holmes' subsequent psychological works of fiction which were "tainted with the physiological." Surely Holmes, far more sensitive concerning his literary reputation than about his clinical ability, would have been disappointed and incensed over having these studies of abnormal characters regarded as case histories. In the light of the development of modern psychiatry they remain as testimony to his medical acuity, his wisdom and psychiatric understanding.

In "Elsie Venner" the theme concerns the effect of pre-natal influence upon the abnormal character development of the heroine. The circumstance that the mother was bitten by a snake during pregnancy is held responsible for the reptilian instincts which Elsie Venner manifested. This interesting theme is still discussed and has points in common with a certain psychoanalytic theory which emphasizes the trauma of birth as the cause for the development of neuroses. The whole subject of pre-natal influence in relation to anxiety has recently been reexamined in the light of observations made during the psychoanalyses of patients.

The second novel, "The Guardian Angel," is a study of hereditary influences on the mind of one individual and postulates that inherited personalities may enjoy "a kind of secondary or an imperfect yet semi-conscious life"—a "co-tenancy" in one body. Holmes maintains that "this body in which we journey across the isthmus between the oceans is not a private carriage but an omnibus."

In Myrtle Hazard, of "The Guardian Angel," the traits and experiences of her antecedents reappear in her and produce strange and unaccountable actions (hysteria) seemingly belonging to the personalities of several ancestors. A similar concept has received wide attention under the term "collective unconscious" of Carl Jung, at one time closely affiliated with Freud. Jung would include as inherited in the unconscious not only the experiences of our immediate ancestors but of the race.

The final novel, "A Mortal Antipathy," is essentially the study of a compulsion neurosis by a fine psychiatrist. Written during the mellowness of Holmes' old age it is a final and unsparing thrust at meddling by the clergy in situations where emotional disturbance is threatening the very existence of the patient. The preface, as the prefaces of the two previous novels, defends the validity of the theme of the story from a

medical standpoint. In it Holmes approaches more significantly the psychoanalytic position of Freud—namely, that an infantile shock or trauma may cause a conditioning in a person which he never outgrows.

In this story Holmes realized that he was presenting a hazardous experiment and that the theory with which he accounted for the mortal antipathy for women of his main character, an otherwise normal young man, could hardly be rendered plausible. In the preface to the book he refers to the case of a "middle-aged man who could never pass a tall hall clock without an indefinable terror. While an infant in arms the heavy weight of one of these tall clocks had fallen with a loud crash and produced an impression which he had never got over."

An atmospheric impression of this kind associated itself with a terrible shock experienced by the infant who is the subject studied in "A Mortal Antipathy." This idea is far too fantastic for Holmes' recognized biographer, John T. Morse, Jr., who in 1896 writes, "From 'Elsie Venner' with her mysteriously envenomed nature to that absurd young man, Maurice Kirkwood, who could not bear the sight of a young girl because his pretty cousin had caused him to fall from a balcony in his boyhood, the downward step was indeed a long one." Holmes states that such impressions could not be outgrown, but might possibly be broken up by some sudden change in the nervous system affected by a cause as potent as the one which had produced the disordered condition—a theory being actively revived today in shock therapy in its various forms.

There cannot be the slightest doubt that Holmes himself is the doctor in each of the three stories of mental aberration—tedious reading as works of fiction. The repressive New England atmosphere produced similar strange physiological manifestations observed by Holmes at the bedside. This repressive cultural attitude lingered on after his death. But the scientific spirit also continued to grow greater and stronger in Cambridge.

Holmes' ideas live in abeyance in New England for twenty-five years after his death. The link which Holmes established between Cambridge and Vienna in 1840 appeared again in 1909. A scholarly and distinguished professor of neurology at Harvard, James Jackson Putnam (1846-1918), whose time of medical activity overlapped that of Holmes, became convinced that the theories of a still unacclaimed Viennese investigator were worthy of thoughtful examination. And so Sigmund

Freud came to New England at Putnam's instigation and at the invitation of Stanley Hall

Freud's lectures delivered at Clark University have become classics for students of psychoanalysis, but I think that Freud himself could not have conveyed the essence of his theory better and more convincingly to the distinguished, yet skeptical and critical audience he faced than these words "There are thoughts that never emerge into consciousness, which yet make their influence felt among the perceptible mental currents, just as the unseen planets sway the movements of those which are watched and mapped by the astronomer. Old prejudices, that are ashamed to confess themselves, nudge our talking thought to utter their magisterial veto. In hours of languor, as Mr Lecky has remarked, the beliefs and fancies of obsolete conditions are apt to take advantage of us. We know very little of the contents of our minds until some sudden jar brings them to light, as an earthquake that shakes down a miser's house brings out the old stockings full of gold, and all the hoards that have hid away in holes and crannies." As you may surmise this was written by Holmes

One wonders why Holmes' ideas did not receive greater attention when they were written. It is probably because society at large was far less prepared to entertain them in 1870 than it was to accept Freud reluctantly in 1900. But this does not explain why Holmes' theories were not more critically tested by two truly distinguished scientists of the Boston group who immediately followed him—William James, the philosopher, and Morton Prince, the psychiatrist. The fact is that psychiatry still remained in a somewhat sterile stage of description and classification. The social significance of mental deviation, so stressed by Holmes, had not been grasped by science or society. Neither, therefore, could give heed to dynamism of thought or appreciate its correlation to the masterly clinical descriptions of Holmes sketched in this presentation.

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NEWER CONCEPTIONS OF POSTINFECTIOUS AND RELATED FORMS OF ENCEPHALITIS*

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THE MEANING OF "ENCEPHALITIS", CLINICAL VARIETIES

THE term "encephalitis" means a disease of the brain. As a result of a prevalent convention of recent origin, and with no sound basis in derivation, the term is confined by many pathologists to conditions characterized by inflammatory phenomena. Once the name has been applied to a certain clinical entity, there appears a tendency to consider that disease as infectious in origin.

There are, of course, infectious diseases of the central nervous system. The most familiar type is that represented by acute brain abscesses, granulomata, and syphilis of the brain. The term "encephalitis" is seldom applied to them, and I shall say little more about them.

Other known diseases in which an infectious agent can be cultivated from the brain are poliomyelitis, typhus fever, the St. Louis, Japanese and equine epidemic encephalomyelitides, encephalitozoon encephalitis, and a few others. Except for poliomyelitis, these conditions are so rare in this community at present as to be curiosities. A peculiar position is occupied by lethargic encephalitis, there was an epidemic twenty years ago. It was generally considered to be an infectious disease, but no proof of its infectious nature has ever been brought out. Cases of lethargic encephalitis are now extremely rare, if indeed any authentic ones occur, and the acute disease is no longer a practical problem.

There is, however, one form of "encephalitis" (so-called), which is perhaps more common than poliomyelitis with paralysis, often misdiagnosed and usually misunderstood. This is the so-called "disseminated encephalomyelitis," neuroptic myelitis, Schilder's disease, acute multiple

* Read October 25, 1940 before the Graduate Fortnight of The New York Academy of Medicine From the Department of Neurology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York City.

Fig 1

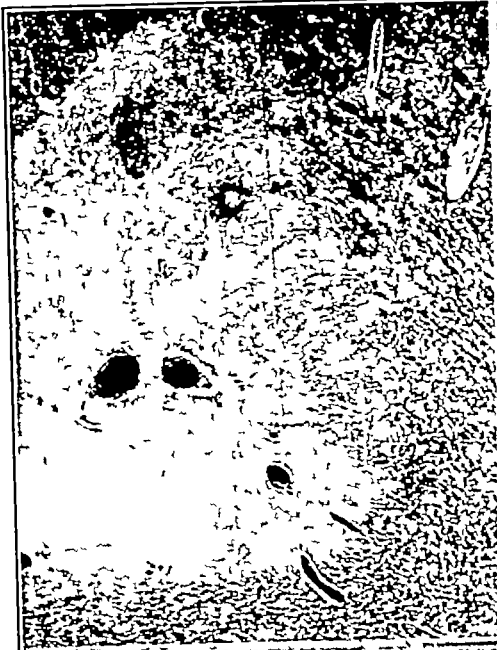


Fig 2



Fig 3

Fig 4

Fig 1—Extreme venous congestion of a convolution of the cerebrum, with perivascular demyelination, from a case of postvaccinal encephalomyelitis. Masson stain, 8 mm lens enlargement.

Fig 2—Diffuse glial proliferation about distended vessels. Encephalomyelitis following sinusitis. Cresyl violet stain, 8 mm lens.

Fig 3—Adventitial infiltration. Post-measles encephalomyelitis. Cresyl violet stain, 8 mm lens.

Fig 4—"Encephalitis" following antirabic inoculation. Cresyl violet stain, 16 mm lens.



Fig 5—Perivascular demyelination Postvaccinal encephalitis Weigert stain, low power

sclerosis, or postinfectious encephalitis. It is related to “acute transverse myelitis.” It is, I believe, a non-infectious disease.¹

PATHOLOGY OF THE “ENCEPHALOMYELITIDES OF THE WHITE MATTER”

Let us begin with the pathology of the condition. In patients dying during the acute stage, the brain is found to be somewhat edematous, but macroscopic changes are otherwise inconspicuous. The sinuses are often thrombosed, the vessels throughout the brain congested (Fig 1).

Microscopically, there is widespread proliferation of glial cells, especially around engorged vessels (Fig 2). In some areas, there are collections of phagocytic cells, occasionally a few resembling lymphocytes, within the adventitia (Figs 3, 4). In small or large areas of the white matter, myelin is destroyed and undergoing phagocytosis, and axis cylinders appear damaged. Damage to cortical cells is variable (Fig 5).

Most of these specimens are from cases of post-measles and post-vaccinal “encephalitis,” since these two varieties are better studied and more often recognized than others.² They are not the most common, however. Exactly the same structural changes are encountered more frequently after pyogenic infections, such as pneumonia, tonsillitis, sinusitis, and the like.³ They may follow German measles,^{4,5} chicken pox,⁶ undulant fever,⁷ inoculation for rabies,⁸ burns,⁹ carbon monoxide

poisoning,¹⁰ administration of sulfanilamide,¹¹ trauma,¹² and other exogenous injuries. Perhaps the commonest of all are the spontaneous cases, coming on often out of a clear sky in previously healthy individuals.

The clinical picture is extremely varied. In severe cases, there are coma, convulsions, meningism and often a picture suggesting tetanus. Hemiplegia, hemiataxia, nystagmus, myelitis, changes in the optic nerves and other signs suggesting involvement of the white matter may occur. Mental and emotional changes may be the presenting symptoms, and abnormalities in neurological examination may be found unexpectedly. The spinal fluid is seldom normal, and usually contains 10 to 2,000 cells, an increased protein (up to 200), normal sugar, perhaps an alteration in the gold sol curve.³

Not enough cases have been collected and published to permit us to say what the mortality is, but it is high—30 per cent in the postvaccinal cases in Bastiaanse's series,¹³ 7 out of 31 cases in Adler's mixed series.³ The remainder recover entirely or with residuals. In an unknown proportion of cases (15 per cent of Adler's series) relapses occur, and the disease becomes recognized as multiple sclerosis.

DISTINCTION FROM ACUTE TOXIC ENCEPHALITIS

Clearly to be differentiated from the group of proliferative and degenerative encephalitides just discussed, are the acute toxic encephalitides (according to Adler's definition) frequently seen as complications of acute infectious diseases, especially pneumonia. The toxic encephalitides may be recognized clinically by the indefiniteness of the picture—coma, delirium, convulsions, muscular twitchings—and the fact that the spinal fluid shows minor changes or none, aside from an occasional slight increase in cells. In fatal cases, acute general cortical edema and swelling of nerve cells are found, but practically no focal injuries or collections of cells. The patients who recover show no residuals.

PATHOGENESIS OF "ENCEPHALOMYELITIS"—OLDER THEORIES

The conventional attitude towards the postinfectious encephalitides and other disorders of the same group, is that they are due to the presence of a virus in the brain. This point of view (first apparently expressed by Pette¹⁴) was based on the presence of cellular proliferation and infiltration, and on the fact that some cases follow virus diseases, such as vaccinia and measles. Prompted by this assumption, material such as

spinal fluid and blood from hundreds of cases (mostly of multiple sclerosis) has been cultured and injected into animals, without a single significant result. Fresh brain from early autopsies in acute cases has been inoculated into the brains of monkeys without infecting them. Bacteriological methods give us, then, completely negative evidence as to the infectious origin of the lesions.

A minority of authors, such as Hassin,¹⁵ speak of the histologic reaction of diffuse perivascular glial proliferation seen in this group of cases as "toxic." There are two objections to this term. One is that the typical reaction is found in certain cases of traumatic injury to the brain, about injuries, and in arteriosclerotic foci, in which the term "toxic" must be given a peculiar meaning, if it is to apply at all. The second objection is, that the term gives us no dynamic picture of the mechanism of the development of the lesions, which could possibly be translated into a policy of treatment.

THE ROLE OF VASCULAR OCCLUSION

It is the purpose of this paper to present evidence for a *third* interpretation of the tissue changes found in the encephalomyelitides involving the white matter, namely, that the parenchymal reaction is one which characteristically follows closure of small blood vessels in the central nervous system, and that the primary change is one in the clotting mechanism of the blood.

There are a number of different pieces of evidence which support this view. Typical "encephalomyelitic" changes may be produced regularly in animals by mechanically blocking venules¹⁶ (Fig. 6), by injecting coagulants such as lung extract or brain extract into the venous circulation¹⁷ (Fig. 7), by poisoning with carbon monoxide, which produces venous thromboses in a minority of instances,¹⁰ or by administration of potassium cyanide, an asphyxial poison.¹⁸ It may be found in human brains in which small vessels have become occluded by arteriosclerosis, trauma, inflammatory thrombosis,¹ or intimal proliferation¹² (Fig. 8).

Turning again to the pathology of the condition, let me remind you that the congestion of the brain is described as a feature of the pathology of the disease by practically all observers (Fig. 1). In acute or progressive cases, thrombi have been described by the majority of pathologists who have made any statements about the contents of the vessels. In my own cases, thrombosis has invariably been found in relation to the le-

Fig 6

Fig 7

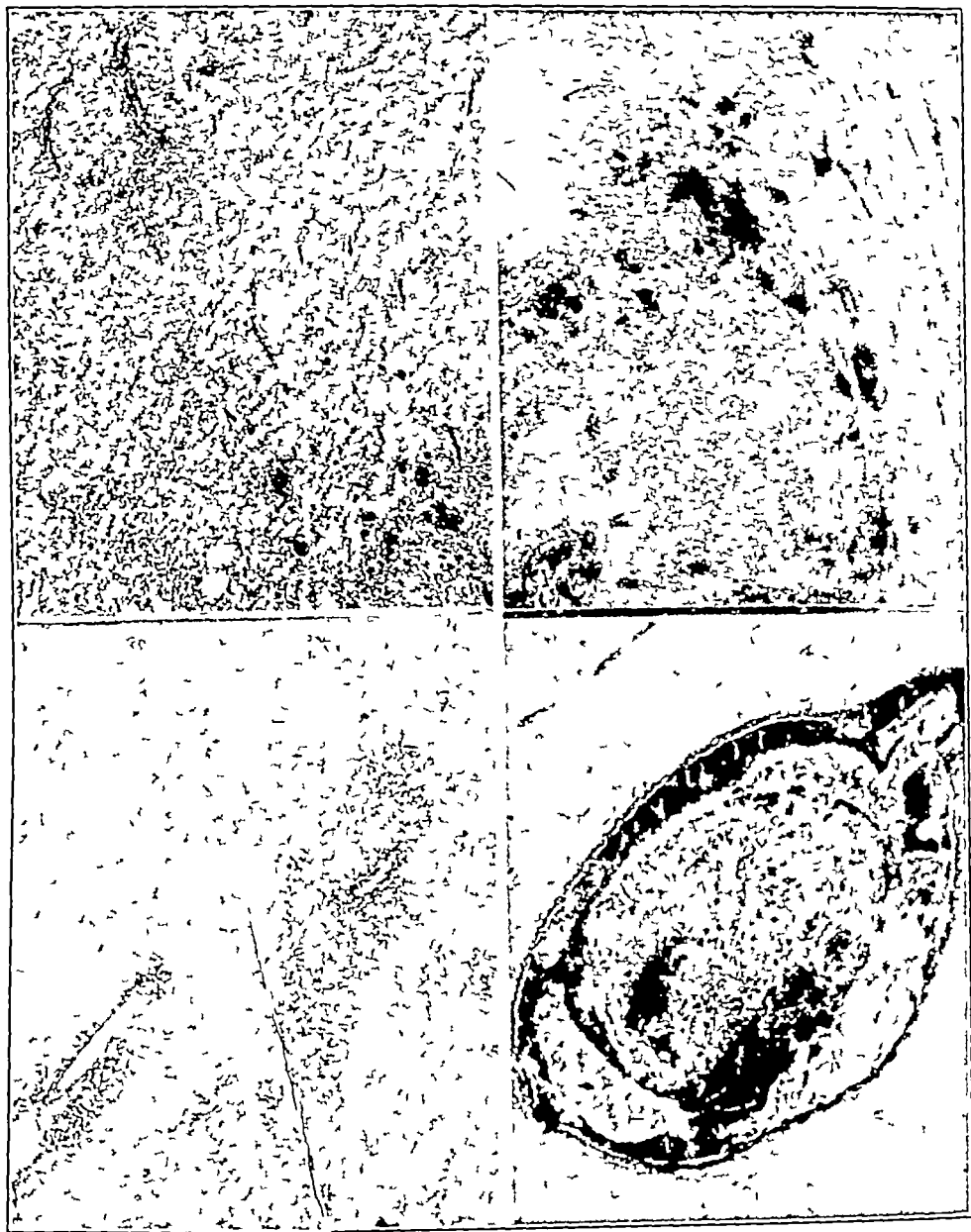


Fig 8

Fig 9

Fig 6—Diffuse glial proliferation in the territory drained by an experimentally occluded vein (in a dog) Cresyl violet, lens enlargement

Fig 7—'Encephalomyelitis' about thrombosed veins, following intravenous injection of a coagulant (lung extract) Gallocyanin stain, lens enlargement

Fig 8—"Encephalomyelitic reaction" in traumatic brain purpura Cresyl violet stain, 16 mm lens

Fig 9—Thrombus in a small vein from a case of postvaccinal 'encephalitis' Mallory's connective tissue stain, low power

sions,¹ and in all the cases in which such an examination could be made, in other organs as well (Figs 9, 10)

Thrombosis of the dural sinuses is a common finding, and on the other hand, parenchymal degeneration of this type is common, though seldom studied, in cases of sinus thrombosis. In the cases in which it has been possible to make a histologic study of the other organs, small thrombi are found in them also. It is only in the brain, however, that such minute clots are likely to produce permanent damage.

In older writings on the subject, it has been customary to attribute the thrombi found in lesions to the inflammatory phenomena about the vessels. If this were the sequence of events, one would not expect the same parenchymal reaction to occur in relation to vascular occlusions of other types, for example, in the experiments which have been mentioned, in arteriosclerotic foci, and in other organs of the body.

THE CAUSES OF THROMBOSIS

If this interpretation of the origin of the parenchymal lesions is correct, the problem, is of course, shifted from the brain to the blood stream. Empirically, the presence of disseminated small thrombi throughout the body in cases of acute terminal infection has been reported by many pathologists. Presumably, similar thrombi occur in patients with the same acute diseases who do not die. If they occur in the brain, the lesions they produce must resemble those we have just reviewed. The strange thing is not that such thrombi should form in the brain in occasional cases, but that they are so rare.

The problem has been brought a little nearer solution by the studies of Finley,¹⁰ who has shown that the onset of postvaccinal "encephalitis" occurs with great regularity on the eleventh day of the disease—the very day when immunity is at its height, and re-vaccination becomes impossible. In a small group of cases, the "encephalitis" appeared on the sixth to eighth days. In all of these, the encephalitis followed re-vaccination, in which the onset of immunity is accelerated. In the post-measles encephalitides also, he found evidence that the onset coincided with the development of immunity.

That the origin of "encephalomyelitis" is in some sense an allergic reaction is indicated also by the experimental production of a characteristic histologic picture by the subcutaneous injection of tetanus toxin²⁰ or of brain extract.²¹ It seems not unreasonable to suppose that an in-

Fig 10

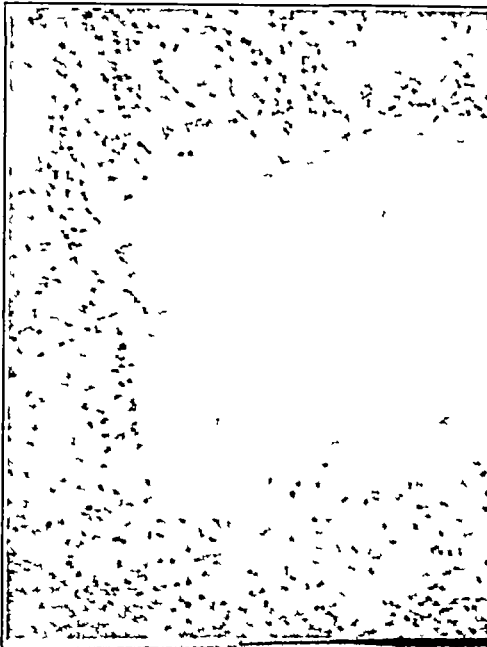


Fig 11

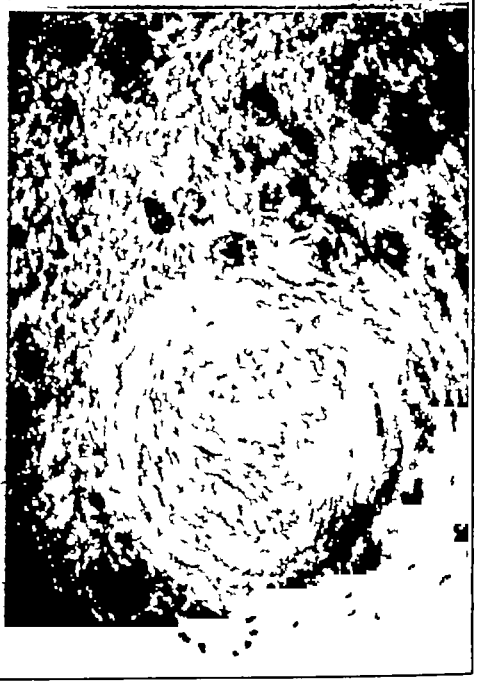
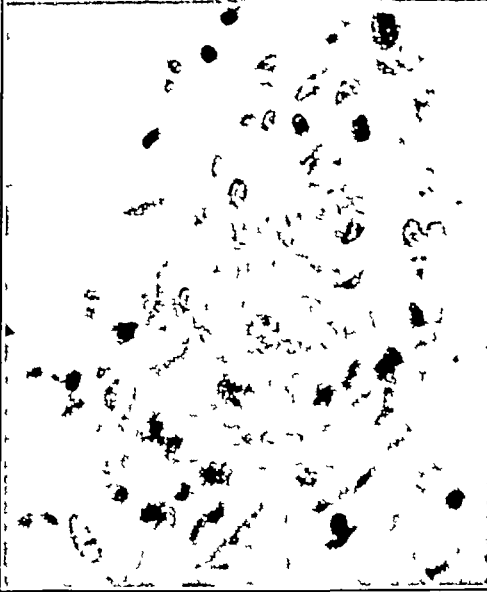
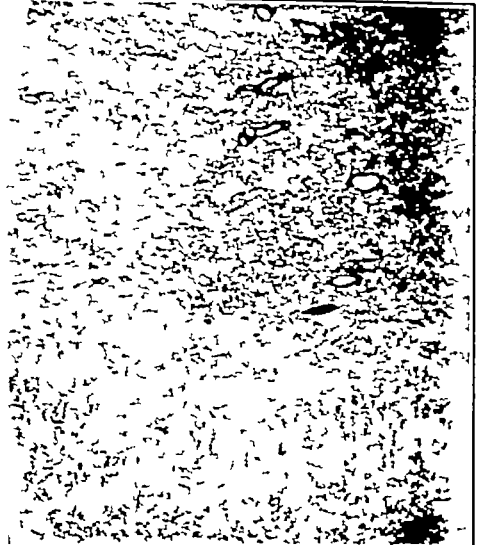


Fig 12

Fig 13

Fig 10—Thrombus in the liver from a case of "encephalitis," following tonsillitis. Hematoxylin-eosin, low power enlargement.

Fig 11—"Encephalomyelitic reaction" in an acute extension of a chronic plaque of a case of multiple sclerosis. Cresyl violet stain, lens enlargement.

Fig 12—Thrombus in a vein draining a fresh lesion, from a case of multiple sclerosis. Masson stain, oil immersion.

Fig 13—Obliterated vessel in an old periventricular plaque, from a case of multiple sclerosis. Masson stain, oil immersion.

stability of the clotting mechanism of the blood might be one aspect of allergy. Tetanus toxin contains a hemolytic substance, and the brain extract employed is an active coagulant.

It has been pointed out that similar parenchymal changes may occur as a result of poisoning with carbon monoxide or nitrous oxide. They are usually ascribed either to a "toxic" action of the gas on the tissues, or to the anoxemia produced. There is reason for believing that neither explanation is adequate, and that in these conditions also, the degenerations occur in the areas of drainage of thrombosed venules. Thromboses are common elsewhere in the body and asphyxia has been shown to favor intravascular coagulation.²²

RELATION OF "ENCEPHALOMYELITIS" TO MULTIPLE SCLEROSIS

Another aspect of the problem of "encephalomyelitis" is that relating to the fate of the lesions. Those which are sufficiently intense end as actual cystic softenings, such as are often seen in carbon monoxide poisoning. The less intense ones, in which axis cylinders are not destroyed, become glial scars. They are then indistinguishable from the plaques of multiple sclerosis, and irregular extensions and exacerbations of the acute stage may occur in them. We may say, therefore, that certain types of "encephalomyelitis" represent the acute stage of a process, which we know in its chronic relapsing state as multiple sclerosis.²³ Acute proliferative lesions, thrombi, and occluded vessels are found in cases of multiple sclerosis (Figs 11, 12, 13). As is well known, the exacerbations of multiple sclerosis, like the onset of "encephalomyelitis" may be precipitated by non-specific infections.

This fact in turn throws some light on the pathogenesis of "encephalomyelitis," for recent studies have shown abnormalities in the clotting mechanism,²⁴ in the proteins of the blood,²⁵ and the presence of an abnormal immune substance.²⁶

THERAPEUTIC CONCLUSIONS

The onset of disseminated thrombosis within the central nervous system is usually rapid, and there is at present no available method of predicting its occurrence. In a small proportion of cases, the disease is progressive. Conceivably, its progress might be halted by administration of anticoagulants, such as heparin²⁷ or cysteine.²⁸ Neither has been tried in encephalomyelitis, but the latter has been given in cases of multiple

sclerosis There is a field for further investigation here

If the cerebral lesions are secondary to a collection of pus, relief may follow drainage of it

One thing seems clear that "antiseptic" treatment, unless directed at the underlying disease, is entirely out of place There is reason for believing that treatment by sera, or indeed, intravenous medication of any kind, is contraindicated, as similar encephalitudes have been precipitated by administration of sera^{17, 20}

A systematic collection of well-studied cases would do much to clarify the situation

SUMMARY

The terms "encephalitis" and "encephalomyelitis" have been used by neuropathologists to denote several groups of diseases characterized by infiltrations and glial proliferations Some of these diseases—the pyogenic and granulomatous infections, and certain epidemic forms such as poliomyelitis—can be demonstrated to be infectious in origin In others, probably forming the largest group, the disease has never been transmitted to animals and cultures are uniformly sterile Typical examples are the postvaccinal and post-measles encephalomyelitudes Similar histologic pictures are seen in certain instances of arteriosclerosis, carbon monoxide poisoning, head injury, etc., and most often of all, after the common respiratory infections or without obvious etiology There are both pathologic and clinical transitions between this group of diseases and multiple sclerosis

Recent studies have made it seem likely that the fundamental abnormality in such cases is a spontaneous thrombosis of small vessels within the central nervous system Such thrombi have been regularly found in acute cases, not only in the brain, but in other organs as well If vascular obstruction of a similar type is produced in some other way, either spontaneously or experimentally, similar parenchymal lesions result The onset of the cerebral symptoms in the postvaccinal and post-measles types corresponds with the height of the immune reaction

The possible bearing of this conception on the handling of cases is discussed

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THROMBOPHLEBITIS *

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THE status of current theories and factual knowledge pertaining to thrombophlebitis and its allied syndromes is at present very confused and decidedly meager. It is not generally known throughout the medical profession whether we are dealing with one, several, or many different diseases. We do not fully understand the etiological factors responsible for the development of the various syndromes so roughly classed under this single heading. The mechanism of development we understand in part, the pathology we can observe, the signs and symptoms are usually, but not by any means always, recognizable. When we reach the problem of treatment, we find ourselves in a state of relative chaos, overwhelmed by variety, confused by conflicting methods and reasoning, pleased by moderate, inexplicable success, chagrined by frequent, unexplainable morbidity and, not infrequently, sudden death.

Each of these problems will be surveyed in turn and I shall attempt to evaluate the various theories regarding them on the basis of experience with more than 300 cases of this condition studied during the past six years.

Of the last 70,000 patients admitted to the New York Post-Graduate Hospital, 182 (0.26 per cent) suffered with thrombophlebitis on admission or during their stay. This incidence in a general hospital population is undoubtedly lower than it would be in an institution with an obstetrical service, although nine of our cases were postpartum. Probably all statistics of postoperative incidence are low, since a considerable, but unknown number of patients leave the hospital and develop phlebitis at home where they remain for treatment.

In our vascular clinic, where all types of vascular problems are studied, of the last 2,400 admissions, 92 (3.8 per cent) have been cases of thrombophlebitis.

* Delivered November 29, 1940 at The New York Academy of Medicine as a Friday Afternoon Lecture

In this combined series of 274 patients, known etiological factors have been as follows

Infection, 63

Varicose veins, 51

Postpartum, 32

Trauma (a) injury, 40 (b) postoperative, 52

Thromboangitis obliterans, 18

The etiology has been unknown in 59 cases

Barker¹ has divided thrombophlebitis into the following groups (slightly modified)

1 Local

(a) Chemical—arsenical or other irritating injections

(b) Mechanical—direct pressure or injury

(c) Local inflammatory thrombophlebitis—part of local lesions, i.e., erythema nodosum, tuberculides, gummas, etc

(d) Suppurative thrombophlebitis—acute infectious, involving the jugular, portal veins, etc

(e) Varicose thrombophlebitis—traumatic or without known trauma

2 Hematogenic Thrombophlebitis

(a) Chlorosis

(b) Polycythemia vera

(c) Leukemia

(d) Pernicious anemia

3 Secondary (complicatory) Thrombophlebitis

(a) Postoperative—(after 16 per cent of laparotomies)

(b) Pregnancy and postpartum thrombophlebitis—(0.5–1 per cent of deliveries)

(c) After severe injuries

(d) Complicating infectious systemic diseases Especially typhoid (3 per cent) and pneumonia (0.6 per cent)

(e) Complicating non-infectious systemic diseases, especially carcinoma and heart disease

(f) Complicating epidermophytosis

4 Primary Thrombophlebitis

(a) Thromboangitis obliterans (40 per cent develop thrombophlebitis)

(b) Thrombophlebitis migrans (88 per cent male—80 per cent under 50 years)

(c) Idiopathic, non-recurring thrombophlebitis

There is a tendency of some individuals to develop serial episodes of thrombophlebitis of various types. Some families have numerous cases in a family just as some families will show a marked tendency to develop varicose veins.

A study of this classification clearly demonstrates that we are in all likelihood dealing with numerous distinct syndromes with individual characteristics as to precipitating causes, physical background, course and probable prognosis. In certain of these syndromes the etiological factors appear quite clear as in chemical phlebitis and suppurative phlebitis. In the first instance the reaction appears to be that of a chemical irritation of the intimal and other layers of the venous wall with a roughening of the lining and most frequently a spasm of the vessel resulting in a stasis with thrombus formation, but without evidence of primary bacterial invasion. In the second, we have the opposite, as for example, with the reaction due directly to bacterial invasion of the jugular vein or the surrounding area from a primary otitis media and mastoid infection. A similar type of bacterial invasion may occur from any form of suppurative organisms involving the adjacent veins.

In most of the types of thrombophlebitis in our classification the etiological factors are more difficult to evaluate. It appears that in most instances several may play a part, as follows:

- 1 By means of trauma, dehydration or other factors, the intimal lining becomes damaged (other layers may be primarily involved—the intima secondarily)
- 2 The blood flow is retarded or blocked by mechanical blockage, as with pregnancy, tight bandages, binders, or varicosities, these factors precipitate a thrombosis by a mechanism described later
- 3 Organisms of a variable or unknown type invade the thrombus through the blood or lymph streams

This brings up the question as to whether these latter types of phlebitis are associated with one or several specific bacteria or not. Thus far, in my opinion, there is no conclusive work demonstrating that any particular organism is universally guilty or even guilty in the majority of instances. Cultures of acutely invaded veins have occasionally shown various streptococci, colon bacilli and other organisms, but these find-

ings are too inconstant to warrant very serious consideration. The frequency of the relationship of epidermophytosis to single and recurrent phlebitis of the feet and legs has been noted in many clinics and has given rise to the speculation that this fungus infection may be responsible, either by direct invasion or an allergic response. Dunham² in our laboratory, has cultured 15 of these veins for fungus growth without obtaining a positive growth in a single instance. The whole picture appears to us as unlike a typical allergic response, especially in those patients who are acutely ill with pain, redness, swelling (not urticarial in type), fever, increased white count and sedimentation rate. A third possibility seems more likely, namely, that organisms, be they bacteria, sub-bacterial forms or viruses, are admitted through the cracks in the skin produced by the fungus and drain upward along the veins or venous lymphatics. Similar drainage may cause phlebitis elsewhere. In our studies Dunham has succeeded in producing in egg chorioallantoic membranes growths which could not be differentiated from typical virus growths from four or possibly six segments of acutely inflamed veins, of fifteen thrombophlebitic veins cultured. From ten control cases none of these growths were obtained. We could not keep these growths alive through more than four passages, or isolate them as definitely virus in nature. Injected into various animals, they did not produce characteristic lesions. We cannot, therefore, reach any conclusions from this work as yet, but feel that if the cultural difficulties can be overcome, it should be more extensively pursued. We are still forced to admit that we do not know the answer to the cultural problem, though most thrombophlebitis certainly appears to be of an infectious nature.

Mechanism Thrombus takes place as a result of several mechanisms operating at the same time and interdependently. There are still great gaps in our specific knowledge regarding this process but in accord with the most acceptable theories the process is somewhat as follows:

The conversion of the soluble fibrinogen to the insoluble fibrin is brought about by a ferment thrombase (thrombin) formed in the plasma of shed blood by the action of calcium ions upon a thrombase precursor called prothrombase (prothrombin). Formerly calcium was thought capable of producing this reaction alone, but Mellanby³ has demonstrated that this conversion is actually effected by thrombokinase in the presence of calcium ions. Though some delay in the formation of the clot may occur in its absence, calcium is not necessary for the coagulation of

thrombase once it has been formed Ferguson⁴ found that during the process of activation of prothrombinase by calcium and thrombokinese, there is a stage lasting for a few minutes in which the removal of calcium (by the addition of oxalate) causes inactivation of the newly formed product ("fresh" thrombase). After the thrombase is fully elaborated ("ripe" thrombase), except for the slight delay above mentioned, the removal of calcium ions does not affect the coagulation. Ferguson believes that this difference in the effect of calcium-lack upon "fresh" and "ripe" thrombase indicates the formation of an intermediate complex in the production of thrombase from prothrombase. He concludes that thrombase (thrombin) is a calcium-cephalon-prothrombase complex or compound. Mellanby⁵ has shown that heparin is an anti-thrombase, not as Howell⁶ believed, an anti-prothrombase. That is, it does not prevent the conversion of prothrombase to thrombase, but inactivates the latter enzyme after it has been formed. The inactivation is dependent upon the presence of neutral salts, for dialyzed plasma *does* clot readily when thrombase and heparin, which ordinarily would not cause clotting, are added to it. Heparin is present only in minute amounts in circulating blood and is not responsible for the maintenance of the fluidity of the blood in the living body. The blood does not clot intravascularly, simply because no thrombokinese is available to convert prothrombase to thrombase. Thrombokinese is present in all tissues, including blood platelets, but is held to be freed and available only under certain conditions, usually involving injury to the cells. An anti-thrombase, other than heparin, appears to exist in the circulating blood. This so-called normal anti-thrombase Quick⁷ believes to be simply serum albumin. Thrombokinese not only converts prothrombase into thrombase, but also neutralizes the action of heparin. Therefore, when thrombase and heparin are present in suitable proportions to maintain fluidity of a sample of blood, the addition of thrombokinese causes coagulation. The result is not influenced by the presence of calcium salts. Mellanby⁵ suggests that heparin in tissues serves as a local anticoagulate, preventing clotting in the small vessels. His hypothesis is that the change is effected by the action of thrombase upon fibrinogen which produces a cleavage of the latter into fibrin and serum globulin. Thus the former theory of blood coagulation must be subject to radical revision.

As these changes leading up to the production of fibrin are taking place, certain other mechanisms must come into play in order to produce

a definite thrombus In the living body a number of factors tend to protect the circulating blood against undesirable coagulation Experiments by Glénard⁸ and Baumgarten⁹ show that under favorable conditions blood may be kept stagnant between two ligatures applied to a vein without clotting if the internal lining of the vessel is unaltered and intact

Friedlander¹⁰ has advanced the theory that some roughness of the intimal lining, be it secondary to injury, or the tiny nodules, described by Dietrich,¹¹ following infection, is usually necessary to provide an anchoring buoy on which a thrombus is affixed when the circulation is affected, especially with a tendency to stagnation Virchow considered a thrombus to be identical to an extravascular clot Zahn (1875)¹² demonstrated the process of thrombosis Following an injury to the vessel wall a collection of white cells and platelets occurs at the site of injury, forming a white head of the thrombus which is fixed to the vessel wall Fibrin plays an important part in this process, all blood elements become involved The blood clot forms and the red "tail" of the clot, which is fixed at one side to the white "head," usually begins by waving free at the other end In small veins the white head is frequently large in proportion to the rest of the clot In large veins it may be so small as to be almost invisible, the red "tail" making up most of the thrombus The complex interplay of all of the factors described plus many others, including the relationships of glucose and the electrolytes, cannot be elaborated in detail in this paper, but have been presented by Friedländer¹⁰ and others It should be stated here that many of the links in our presentation must rest thus far on reasonable hypothesis rather than established, factual evidence

The movement of the blood through the veins is dependent on many factors, including the sucking power of the regular pulmonary respirations which draw the venous blood toward the chest The venous valves prevent the blood from slipping back when the intrapulmonary pressure increases The skeletal musculature also acts by pressure on the vessel walls to press the blood along centrally Here again the venous valves make this a one-way process Two factors of slight, if any, importance are the pressure from the arterial side—*vis a tergo*—and the sucking power of the right atrium of the heart

These valves, which are so useful, are damaged by trauma and infection and are frequent sites of thrombosis The thrombus usually forms

rapidly and organization may begin to take place in from 24 to 48 hours. Involution then proceeds during the following weeks by a process of partial fibroplastic organization and partial liquefaction. Eventually, there is usually some return of function of the vein, but this is apt to be incomplete, especially since, as Edwards¹³ and others have pointed out, the valves rarely escape destruction.

The above description deals with thrombosis as it occurs in association with intimal changes in thrombophlebitis. It should not be forgotten that all of the layers of the vein wall are usually involved in this inflammatory process. Indeed Homans¹⁴ maintains that there is usually obstructive involvement of the perivenous lymphatics during the acute stage. In certain cases the inflammatory reaction is practically confined to the adventitia and outer layers without the production of thrombosis, thus, periphlebitis.

Pathological Physiology The pathological physiology resulting from thrombophlebitis is interference of the return blood flow to the heart in the particular venous tree or section involved. This may not be important if small branches are involved, since there is a great abundance of venous collateral vessels draining most of the tissues of the body. When large trunks are involved, however, serious secondary effects are frequently noted. If, for example, the iliofemoral or axillary veins are involved and obstructed by a thrombus extending a considerable distance, the distal venous pressure at heart level may be quadrupled. In the instance of the iliofemoral vein, if the patient stands, the venous pressure may approximate the arterial diastolic pressure. This inevitably produces intense congestion of venules and capillaries and subsequent transudation with edema. Homans¹⁴ has held that obstruction of the perivenous lymphatics is the major factor, in the formation of this edema. We are inclined to agree with Barker¹ that, especially in the early stages most of the edema is probably due to capillary congestion with a marked disturbance in the normal downward gradient of intracapillary pressure preventing the usual reabsorption of tissue and intracellular fluids into the capillaries. The fact that ligation of a large venous trunk does not produce edema is not adequate proof of Homans' theory, since thrombophlebitis most frequently inactivates an extensive portion of the involved vein by either thrombosis, reflex spasm or both, thus usually blocking the return flow of additional collateral vessels. It is probable that persistent chronic edema may be in large part due to the blockage

of the perivenous lymphatics which may be a factor long after the venous balance has been restored toward normal by means of canalization and collateral activation. This latter process results in dilatation of the collateral veins which often overdilate, producing huge varices due to the excessive burden thrown on their relatively weak valves and walls. This produces a vicious cycle, since the valves are overstretched, becoming insufficient. This produces additional reverse pressure on the venous walls and increased stagnation as the valves fail to hold the blood. This is especially serious when the very important saphenous valve at the femoral vein is insufficient, since then the entire venous pressure of the femoral-vena cava system reverses on the weak saphenous veins. This insufficiency of the valves may likewise occur following destruction of the valve leaflets by the process of thrombophlebitis.

I have described these basic phenomena at some length, because the clinical symptoms and signs are of necessity dependent upon them and because any rational therapy should be considered in the light of its effect on them.

THE SIGNS, SYMPTOMS AND COURSE OF THROMBOPHLEBITIS

The signs and symptoms associated with the syndromes of thrombophlebitis vary markedly with the type, location and extent of the lesion. I shall not attempt to describe every possible combination in detail, since the variations are almost countless. Certain important signs and symptoms are briefly noted. After trauma, postoperatively or in association with pregnancy, the physician is on the watch for the development of thrombophlebitis but it should be noted that it may develop insidiously without a known precipitating factor. Cases in this latter group are frequently missed until serious damage has occurred.

1. *Pain* The patient most frequently notices pain at the site of venous involvement. This pain may be slight, as in the instance of involvement of a small segment of an unimportant superficial vein, or moderately or extremely severe if large venous trunks are involved. It may be described as a sense of soreness in the local area or it may be referred, as in several patients with iliofemoral venous involvement, to the back, in the lumbosacral area. Differential diagnosis must sometimes be made between this syndrome and an abdominal or psoas abscess and acute osteomyelitis of the spine. In addition to local referred pains we see in patients with migratory phlebitis the same types of pains involving vari-

ous venous branches throughout the body. Any branch may be involved although a thrombus does not necessarily occur at the site of each painful area. We feel that it frequently happens that the lesion may be essentially periphlebitis, involving the outer layers and producing a painful syndrome without thrombus and edema, as contrasted to other episodes representing thrombophlebitis where the thrombus and edema are the main features but the pain is minimal. In many instances these are combined. One additional form of pain—general malaise—is very frequently a major factor. Contrary to the theories of Meyer,¹⁵ the pains of phlebitis should not be related to those of rheumatism or “growing pains.” What is needed is more clear-cut differential diagnosis and constructive thought on this subject rather than additional confusion.

2 *Tenderness* Associated with the local pain is tenderness, which in general extends along the course of the involved veins. This tenderness is more diffuse when deep veins are involved but at certain areas where the veins may be pressed upon more directly, the tenderness is more acute. These areas include the inguinal area, Scarpa’s triangle, Hunter’s canal, the popliteal space, directly back of the middle of the calf, and others.

3 *Cramps* A form of pain not often mentioned is that produced by very severe muscular cramps occurring rather frequently in patients with deep vessel phlebitis. These may be of extreme severity and seriousness, since it may be virtually impossible for the patient to lie still while the cramp is present and the cramp may, by exerting distorting pressure on the vein, loose an embolism. These are especially apt to occur in the calf muscles, but may affect any sets of muscles in the body.

4 *Color Changes* The occurrence of a superficial thrombophlebitis is almost always accompanied by local redness of the skin directly over the area of inflammation and often extending as a red streak over the course of the vein. It may occasionally spread as a diffuse area of redness, often somewhat resembling erysipelas. Several such patches may be seen in different portions or branches of the same venous tree. In migratory thrombophlebitis patches of this type occur at widely scattered areas far from the primary site. As the acuteness of the local process subsides these red patches gradually turn to a purplish brown and then a dull brown as they fade.

Another type of color change of serious significance may on rare occasions. The periphery of an extremity p

pale bluish or blanched, due to a spastic occlusion of an artery, which rests against the acutely inflamed vein. This may be so serious as to result in massive gangrene, as in the woman reported by Gregoire (quoted by Homans¹⁴) in which instance exploration confirmed this state of affairs. Pallor may also be seen in cases of milk leg, due to blockage of the iliofemoral veins and lymphatics, with resultant pale edema.

5 *Local Swelling* Accompanying the redness, above described, is usually a mild degree of swelling. A lump or, more frequently, a cord-like mass, is palpable along the course of the vein. This type of swelling is not always present and frequently cannot be felt in patients in whom deep veins are involved.

6 *Edema* Congestion of the entire venous and capillary bed distal to the site of blockage, in varying degrees, inevitably follows thrombosis. This may be quickly adjusted, especially if the thrombosed vein is small and if collateral venous return is adequately available, as in the instance where veins of the foot and calf are involved. The opposite extremes are seen with blockage of the larger veins, especially the femoro-iliac veins, resulting in phlegmasia alba dolens, or milk leg. The edema is, as above explained, due to the increased pressure in the venules, capillaries and lymphatics which disturbs the downward pressure gradient and hence interferes with the reabsorption of tissue fluids into the vessels. Edema was present in 92, or 33.5 per cent, of our patients.

7 *Fever* may or may not be present. It is difficult to explain why with three patients with seemingly identical degrees of involvement one will develop a fever of 103° to 105° F. with chills, the second will run a low grade fever of 100° to 101° F. and less commonly, the third will develop practically no fever at all.

8 *Tachycardia* Tachycardia is a frequent sign even in the absence of fever. If persistent, it is considered evidence of continued activity of the disease.

9 *Sedimentation Rate* The sedimentation rate is likewise unpredictable. In some patients it will fall more than 100 mm. per hour (Westergren method), whereas in other patients whose veins appear to be more severely involved, the rate will be well within normal limits (less than 16 mm. per hour). There does appear to be some rough parallelism between fever and the sedimentation rate. In patients with a normal rate it is of no value. Where it is found to be high it seems to be an aid in determining the rate and degree of recovery. We cannot explain the

difference in occurrence of this finding. Perhaps it is due to difference in the degree of tissue destruction or, again, we may be dealing with different diseases which we cannot as yet clearly differentiate.

10 *The Blood Count* The blood count, likewise, may or may not be affected by thrombophlebitis. The white count may rise to 40,000 or more with a high polymorphonuclear count, many young forms and toxic granulations present. We have seen profound anemias develop with red cell counts of under 3,000,000 and hemoglobin of less than 40 per cent. In contrast, I have helped to care for one patient who suffered from migratory phlebitis for more than nine months without definitely abnormal changes in the blood count or sedimentation rate.

It is worthy of re-emphasis that thrombophlebitis may occur in any vein in the body and that symptoms may vary accordingly. Thus, manifestations of liver, kidney, mesenteric, pulmonary and cerebral phlebitis are not uncommon, but are frequently not recognized as such.

COMPLICATIONS AND SEQUELAE

One of the most common and most dreaded complications of thrombophlebitis is pulmonary embolism. The serious cases which result in sudden death, or marked pulmonary signs and symptoms, including sudden pain, the coughing up of bright red blood and the development of typical signs of a patch of pneumonia are usually recognized. I should like to emphasize on the basis of our experience and the experience of others, both in living patients and at the autopsy table, that in all probability more than half of all pulmonary emboli are missed entirely or wrongly diagnosed. This situation can be measurably improved by greater attention being paid to any and all chest symptoms and signs occurring during postoperative or postpregnancy periods, and especially during known active phlebitis. More frequent x-rays in doubtful cases might help, but unnecessary moving of these patients is risky. It should be pointed out that many fatal emboli occur without clinical evidence of phlebitis. Emboli are released in one of several ways:

- 1 A portion of the tail of a fresh thrombus may break loose due to some increase in rate of flow or a twist of the vein, as in one patient with typical thrombotic tendency of leukemia who developed a pulmonary embolism after an osteopathic treatment.
- 2 The thrombus may extend from the vein in which it develops into the lumen of the venous trunk into which the vein drains. If the cur-

rent is strong enough to break off a piece of the tail, in a fraction of a minute we have an embolus

- 3 Occasionally, because of very slow organization of the thrombus, or in suppurative thrombophlebitis, a friable portion will break loose, thus becoming an embolus

Barker¹ cites a large series of patients with postoperative iliofemoral thrombophlebitis in whom fatal pulmonary embolism occurred in only 5 per cent. In half of these it occurred within four days and in the other half it originated from an unrecognized fresh thrombus from the opposite vein. The incidence of embolism in recurrent thrombophlebitis is, in his series, approximately 12 per cent, of fatal embolism, 7 per cent. In our total series pulmonary embolism was recognized in twenty-three (8.7 per cent) patients, of whom six died. There were also eleven emboli to other parts of the body.

The scope of this paper does not permit more than mere mention of the very important and frequently disabling chronic aftereffects of thrombophlebitis. These include varicose veins of all degrees, chronic edema, varicose and other postphlebotic ulcers and chronic eczema, pigmentation, or other skin changes about the ankles. These sequelae have been made the subject of previous papers from our clinic and elsewhere.

Mention should be made of the pains which persistently recur in the previously involved veins, especially with weather changes and on prolonged standing. These are not accompanied by activity of the disease, but may occur at lengthening intervals and with diminished intensity for some years after an acute episode.

The syndrome of postphlebotic neurosis has been described by Allen and Brown.¹⁰ This is seen most often in nervous women who have been in bed for a prolonged course of treatment and who have been overimpressed with the probability of permanent disability or pulmonary embolism. Characteristically, there are few signs of venous insufficiency. The complaints are most often of marked weakness and rather nebulous shifting pains, involving many areas in the body, not confined to previously involved veins.

TREATMENT OF THROMBOPHLEBITIS

As emphasized in this resume, the treatment of this group of diseases is for the most part in a chaotic state of contradictions, claims and counterclaims. Our endeavor will be to face this problem with complete

frankness and reality, differentiating fact from hypothesis, and theory from clinical results. One of the greatest sources of error has been the trend of investigators and clinicians alike to treat these diseases as a single clinical entity. Nothing could be more incorrect in clinical approach or more inhibitory to investigation.

It should be remembered when reading of the virtues of any form of therapy for the *prevention* of thrombophlebitis, that it only occurs in from 1.5 to 4 per cent of all surgical cases, and that any claims of this nature must represent studies of hundreds or even thousands of surgical cases to be statistically sound. Claims as to curative therapy should also be subject to close scrutiny, since the disease is often self-limiting or cured by rest alone. It is frequently difficult to determine in advance which cases are going to be progressive and serious and which will clear up regardless of the therapy used.

I mention a case in point. A patient was desperately ill with migratory phlebitis, which began in a vein over the dorsum of the foot and spread to involve segments of almost every venous tree in the body, including the pulmonary, cerebral, splenic, mesenteric and other internal veins and innumerable superficial areas. Approximately forty specialists saw the patient during nine months. Every test was performed which might have a direct bearing on the phlebitis or any possible causative factor, without producing facts of significant value. Treatment of great variety was tried, including heat and cold, fungicides, abstinence from tobacco, several members of the sulfanilamide group, heparin, fever therapy, metholyl iontophoresis, short wave, almost ad infinitum, with essentially no effects on the course of the disease. We had about exhausted the possibilities. Then he developed mumps of a severe nature with orchitis. His temperature rose to 103.5° F. He became very ill, things looked black indeed. Suddenly his fever dropped to normal by crisis and he promptly recovered from his mumps. More important, his active phlebitis had disappeared and he made a complete recovery, much to his doctors' amazement and relief. It may be significant that mumps is a virus disease.

The treatment of thrombophlebitis may well be divided into (a) preventive therapy, (b) conservative therapy, and (c) radical therapy. Our discussion must be limited to the problem of the acute phases, the chronic manifestations being sufficiently important to warrant a complete lecture in themselves.

Preventive Therapy has for a major objective the prevention of stasis, especially as it may occur postoperatively. The following techniques have been used

1. The use of reflex heat postoperatively as a routine procedure appears sound physiologically and practically. This may be achieved by the use of a heat pad covering some portion of the body. This will increase the rate of blood flow. It may be used constantly, although half hour periods of rest are suggested every three or four hours. Recently Edgar Allen and his coworkers have described an electric heating sleeve to surround an arm or leg during the first few days postoperatively.

Thyroid extract was suggested for the same purpose some years ago. It was reasonable, but probably not as effective and has gone out of fashion.

2. The proper position of the extremity has long been considered settled with the term "elevation." It is superfluous to quote the innumerable advocates of this stand. Friedlander¹⁰ has attempted to standardize the position in order to obtain the most completely free drainage of the veins and lymphatics. He has rightly pointed out that the course of the femoral vein in the prone position is a decidedly uphill one from the popliteal space to the inguinal area. In bedridden patients, therefore, he compensates for this by using the following position. Elevation of the thigh to an angle of 45° and the bending of the knee so that the lower leg is parallel to the mattress, with the heel slightly higher than the knee to insure a steady downhill flow of the blood and lymph. There should be no outward rotation at the hip, thus minimizing angulation and muscle pressure. This has been advocated as a preventive as well as a conservative form of therapy. Recently Frykholm,¹⁷ of Sweden, has investigated the original site of thrombosis and has obtained results strikingly different from the doctrines of Virchow and Aschoff, who held that the commonest site of origin was the femoral vein and its valve pockets. He found in his series that by far the greatest number of thrombi occurred in the veins of the calf and adductor muscles. He reasons that this is due to the fact that while lying in bed the greatest pressure comes on these areas, the veins tend to collapse and after a period of time the intima becomes injured by pressure and thrombosis takes place easily. Logically, according to his conception, the position of elevation, as generally used and described above, would be the worst possible position. He therefore advocates that for from one to two hours daily the head of the

patient's bed be raised eighteen inches. This fills the veins, producing distention, and in addition the calf and adductor muscles are used as the patient slides down against the foot of the bed. He states that none of the patients treated this way developed thrombi but does not state the size of his series, so that the statistical significance cannot be evaluated. Ochsner and DeBakey¹⁸ and many others feel that this position encourages stagnation of the blood and hence tends to produce thrombosis. It should be pointed out that Patey¹⁹ suggested this technique in 1937.

Thus far, you must take your choice of these two approaches. We have not had sufficient experience with Frykholm's technique to pass judgment as to its value in comparison to the technique of elevation.

3 The need for mobilization postoperatively has been recognized for more than forty years.^{20, 21} Activity of the muscle groups may be undertaken by careful, planned exercises in the above mentioned positions. Procedures as radical as walking the patient *from the operating room, even after laparotomies*, and daily after that, have been advocated, especially in eastern Europe. Here I enter a plea for a return to sanity, but patients should be encouraged to move their extremities frequently, in order to decrease the tendency to stagnation of the blood.

Normal respiratory action produces negative pressure for the venous system and increases the circulatory return flow. Postoperatively this tends to be decreased, producing another factor in favor of stagnation. Patients should be urged to take at least ten deep breaths an hour and if necessary $C O_2$ should be used as a respiratory stimulant.¹⁸ This should not be done if there is any question of a thrombosis actually having been started, since, as pointed out by Friedlander,¹⁰ this powerful suction may greatly increase the risk of pulmonary embolism by breaking the thrombus or a portion of it loose into the blood stream. Here every effort should be made to *prevent* deep respiration.

4 The avoidance of dehydration postoperatively by adequate total fluid intake is important for numerous reasons as suggested by Collier and his co-workers²² and others. Dehydration increases viscosity, favoring circulatory retardation and thrombosis.

5 One of the most common causes of retardation of venous blood, postpartum or postoperatively, is the use of very tightly applied adhesive strapping or other types of binders. This is especially serious across the inguinal region, compressing the femoral veins directly and possibly the pelvic veins indirectly. This we believe may well be a factor in the fre-

quency of initial phlebitis in this area. The prevention of this and all overly tight bindings wherever they may produce pressure on veins is important.

6 The use of heparin for the prevention of thrombophlebitis has received its main impetus from the work of Crafoord³ and of Murray and Best⁴ and their collaborators. They have shown that the administration of sufficient heparin to prolong the clotting time will prevent the development of white thrombi and that in experiments where a given amount of injury initiates thrombosis, this can be inhibited by heparin. They are therefore encouraged to believe that the occurrence of thrombosis and thrombophlebitis can be markedly diminished postoperatively by its use. As pointed out in this paper, enormous numbers of surgical cases would be necessary to establish this as a fact, and the technique of administration is somewhat elaborate, so that its routine administration is not feasible. We have been using it in cases of vascular surgery, such as the repair of a false or ruptured aneurysm, embolectomy, and the repair of arteriovenous aneurysms. In some instances the interior of the vessels have been flushed with the pure solution. In addition, it is given intravenously in saline, preferably as a continuous infusion. As supplied now, each 5 cc ampule contains 10,000 anticoagulant units. Two to four or more ampules are added to each 250 cc of normal saline. The clotting time should be checked every hour or two by means of the glass bead method and should be kept, if possible, between 15 and 45 minutes, using more or less heparin as indicated. Heparin as a curative agent will be discussed later. Too prolonged a clotting time may be associated with hemorrhagic risks. Discontinuance of heparin will usually bring the clotting time to normal within 30 minutes. Protamine solution will, in cases of emergency, act as a more prompt antidote.

7 The use of hirudin, the active principle of leeches, as coagulant factor has been suggested by Mahorner and Cechalier²⁶ and Rouhier.²⁷ In our experience this is of doubtful value; this is confirmed by the work of Mayer and Gottlieb, Quentzler,¹⁰ who have calculated that a man of sixty kg would require hirudin of four hundred leeches to prevent clotting at 22

8 The use of sodium thiosulphate intravenously of the thromboembolic syndrome postoperatively has been suggested by Bancroft, Stanley-Brown and their associates.²⁸ In patients who are potential "clotters" is determined

and fibrinogen tests, i e., those who show a high plasma clotting index and high fibrinogen, 10 cc of 10 per cent solution of sodium thiosulphate is administered intravenously on three consecutive days and repeated after an interval of one day, if the above mentioned factors still show a clotting tendency. While these authors rightly point out that no one can predict whether any patient is going to develop thrombosis or thrombophlebitis, they have been encouraged by their preventive results in a large series of postoperative cases.

9 In persistent, recurrent and migratory thrombophlebitis the abstinence from tobacco seems important. It appears clinically to play a part in the tendency to recur in certain patients. Of greatest importance is the fact that in approximately 40 per cent of patients with thromboangitis obliterans, thrombophlebitis occurs and that in a high percentage of these the initial syndrome is that of recurrent attacks of phlebitis. No one can be sure which of these cases is going on to develop thromboangitis obliterans and we know that the omission of tobacco is vital in the prevention of the extension of this disease. I have recently reviewed the evidence for this stand.²⁹ It is certainly worthy of very serious consideration in this group of cases and we make total abstinence a definite rule for our patients.

10 A relationship between the incidence and recurrence of thrombophlebitis of the lower leg and foot and epidermophytosis has been remarked upon in several clinics, including ours. Certain workers believe that the phlebitic syndrome is an allergic manifestation to the fungus, but I find this difficult to accept, because of the type of local and systemic reaction produced. It appears more likely to have an infectious basis. As stated above, Dunham² has cultured pieces of the inflamed veins of fifteen such cases but no evidence of fungus growth has been obtained. It still seems likely to be due to some organism as yet undetermined, but the splitting of the skin by the fungus offers an excellent opportunity for the admission of many organisms. The prevention of subsequent attacks seems to be favorably affected by the treatment of the epidermophytosis. This, however, must again be treated statistically to be positively established. We use potassium permanganate, 1/7000, foot-soaks for 30 minutes daily and later on alternate days, long after the previous attack has subsided. Whitfield's ointment, one-half strength, has also been helpful.

11 The corrective treatment of any blood dyscrasia which tends

toward thrombosis should be undertaken. It may not be possible to achieve success, as in certain cases of leukemia. In some conditions it may not be advisable to return the count to normal levels. Each case must be studied on its own merits. A patient was referred to us for the treatment of his recurrent thrombophlebitis. A blood count revealed the presence of a polycythemia vera, with 8,500,000 RBC and 126 per cent hemoglobin and other findings in proportion. The significant point for this paper is that this patient develops thrombi whenever his blood count is above 4,500,000 with 75 per cent hemoglobin, but none when it is below 4,000,000 RBC. He feels best and generally stronger when we keep his red cells at about 3,000,000, and he is definitely safer. We have used acetylphenylhydrazine in carefully regulated, frequently adjusted dosage to control his polycythemia vera. This constitutes preventive treatment in this patient.

Conservative Therapy Once a thrombus or thrombophlebitis has begun, certain changes in approach should be undertaken.

1. Heat versus cold. The constantly recurring discussion regarding the merits of heat and cold therapy in medical practice has been a source of much controversy in the treatment of phlebitis. More recently the use of heat seems to be more popular on the basis of (1) reducing the spasm and the extension of the thrombosis to nearby veins, (2) encouraging collateral circulation and (3) hastening normal involution of the lesion. These are all good theoretical reasons, but in actual practice we have seen numerous instances where the lesion continued to spread with the use of heat, but promptly regressed, clearing up quickly, upon the application of cold. This has happened frequently enough to appear to eliminate the factor of pure coincidence. We have therefore adopted the policy of starting with one of these agents, but if the trend of the disease is not favorable after a reasonable trial, shifting to the other. If heat is to be used, adequate hot, wet packs should envelop the entire limb. Barker's¹ technique is suggested. The skin is covered with petrolatum and then gauze. Blanket material soaked in hot water, then wrung out, is wrapped around the leg. This is surrounded by a rubber sheet and hot water bottles outside to keep in the heat. This must be changed as often as necessary to provide heat. Dry heat does not appear to be as satisfactory.

If cold is used, it should be in the form of an ice cap applied locally over a towel, on alternating hours.

It is entirely possible that rest does the work for which these agents are credited

2 Probably the greatest source of disagreement arises between the two schools of thought—one advocating immobilization in bed with only mild movements, the other advocating compression bandages with unlimited activity. The policy to be followed must be decided early in each case, since the greatest danger from emboli comes with a program of rest for a few days, then activity before the thrombus has been completely fixed and fibrosed. The advocates^{10 15} of unrestricted activity usually advise the application of compression bandages. They claim that embolic phenomena never occur with unrestricted activity and Meyer¹⁵ insists that the patient *must* walk daily for a distance of three miles in sections of at least one-half mile. The theory for this approach rests on the desirability of supporting the venous walls while encouraging the muscles to pump the blood along, thus increasing the circulation and preventing tips of thrombi from extending out into the lumen of the next vein. The bandages and muscular contraction also tend to fix the thrombus to the wall of the vein. By some formula of theirs the 7 to 9 hours the patient spends in bed at night are not thought to result in extension of thrombi. There are several things wrong with this theory as it applies to general use. In the first place, many patients, especially post-operatively, are entirely too sick to indulge in this activity. In the second place, it cannot apply to phlebitis, as it occurs elsewhere than the leg and thigh. In the third place, emboli do occur following this form of treatment. I have seen such instances in consultation. And lastly, I should like to recite a case history to exemplify how wrong it is to become so intrigued with a particular form of therapy that the patient is forgotten. A delicate elderly lady developed a mild case of phlebitis of one of the veins on the lateral aspect of her right ankle. She visited one of these gentlemen who bandaged her leg firmly and said "walk three miles a day," as he ushered her out. She had not walked three miles a day for many years, but now with a painful leg she proceeded to attempt it. After four days she was in a state of collapse, her temperature was 104° and the phlebitis had extended to her groin. She was desperately sick for months. This is why we advocate a careful study of each case without adoption of fads, but rather the treatment of each patient as indicated. There may be a few patients with a mild local involvement who will tolerate exercise with proper support, I have seen such cases

In my experience they represent a minority, but because the percentage of pulmonary emboli is really fairly low, many patients do escape regardless of the treatment. If a compressive bandage is applied, it should be done with great care so that the patient experiences no pain or discomfort after the application. Various preparation bandages of zinc gelatin or elastic twill bandages have been used. Do not make the mistake made by one physician who went a step further by bandaging a rubber sponge over the inflamed vein, thus massaging it at every motion with very disastrous results.

For most patients it seems wiser to adhere to the conservative rest policy with the position of the leg elevated as previously described. The technique of lowering the leg several times a day is preventive rather than curative. The rest should continue for three weeks or more, depending on the clinical response. In patients who have a high sedimentation rate (and not all do) the sedimentation rate should be normal one week before allowing them up. Mild muscular exercise in bed should be encouraged, but no massage. Friedlander¹⁰ advocates a compression bandage in bed and here it may be of some help in fixing the thrombus in place.

3 We have been using sulfanilamide, sulfapyradine and sulfathiazole in these conditions during the past two years. The clinical results seem encouraging. There are instances however, where they have been useless and we cannot say as yet that their value is definitely proven. Four chronic, persistent cases have apparently been completely cleared up by a course of sulfapyradine for one month. Two have failed to respond.

4 In a small series of cases of thrombophlebitis we have used heparin. It has appeared to speed up the clinical improvement, but the numbers were too small to warrant conclusions.

Murray and Best²⁴ reported twenty-eight patients with no emboli and more rapid clinical improvement. They have since increased their series, but it is still small for statistical treatment. The therapy is continuous and trying to the patient, so that we now reserve it for patients who have had an embolus or whose disease is very actively spreading. Here it has appeared to change the course of the situation favorably in several cases under our observation. It is administered as previously described.

5 Inasmuch as we have failed to see any response to the use of leeches in a number of patients, I shall not discuss it further at this time. Sodium thiosulphate is used as a preventive but Bancroft²⁸ does not feel

that it is of value after thrombophlebitis has begun and we share that opinion

6 Murphy³⁰ and Sokolov and Meyers³¹ have reported favorable results and have recommended the use of Mecholyt iontophoresis in the treatment of active thrombophlebitis. We have tried it on a small series of cases with some encouraging results, but the series is too small to permit conclusions

As we have previously demonstrated³² it is of value in handling the chronic aftermath of this syndrome, but that is another chapter

7, 8, 9 For the reasons described above, the abstinence from tobacco, the treatment of epidermophytosis and the treatment of blood dyscrasias should be undertaken where indicated and by the methods outlined

10 The use of the technique of sympathetic ganglion block with procaine hydrochloride as a conservative form of therapy has recently been advocated by Ochsner and DeBakey^{18, 33}. This was inspired by the work of Leriche and Kunlin³⁴ and their co-workers. It is based on the fact that vasospasm is frequently one of the most important factors in thrombophlebitis from the viewpoint of production of pain and disturbance to the venous circulation and reflexly by affecting nearby veins and even arteries and sometimes this may simulate arterial embolism. The lymph flow may also be retarded. The object in interrupting the vasoconstrictor impulses by infiltration of the sympathetic ganglions with procaine hydrochloride is the reestablishment of the normal exchange of intravascular and perivascular fluids and a breaking up of the vicious circle. Ochsner and DeBakey have reported favorable results as follows: Pain was relieved within one-half hour after the first injection in 86.3 per cent of cases and in the remainder after the second injection. This relief was permanent. More than 50 per cent of the patients were free from fever within 48 hours after treatment. Forty per cent of the patients showed subsidence of edema within 4 days. Two-thirds of the patients were discharged from the hospital within 8 days and 90 per cent within 12 days. One patient out of twenty had a pulmonary embolism. They state that in follow-up studies for from 4 to 12 months there has been no recurrence of edema or other postphlebotic manifestations. These are indeed remarkable figures. In other hands the results, while encouraging, have not been quite so good. I know of two cases of pulmonary embolism in one series of five cases. While the symptom complex may

be changed, it is difficult to see how this, *per se*, would affect the actual inflammatory process of a thrombophlebitis, including the development of a growing clot. Is not the tendency to move about early inviting added risk of embolism? Their series shows a very low incidence, but the number is again too small for statistical interpretation.

11 *X-ray Therapy* Mention should be made of x-ray therapy, as used by Carty and others. This technique has apparently been successful in arresting the progress of certain cases of thrombophlebitis. Our experience with this method is extremely limited, but I have seen several patients in whom it was successful and a few others in whom it failed. It is only fair to say that the limited use of this method to date prevents any final conclusions as to relative merit as compared with other forms of treatment.

THE RADICAL THERAPY OF THROMBOPHLEBITIS

Conservative therapy is usually adequate. In some instances, because of location, a radical approach is not feasible. Occasionally, with an actively progressive lesion, especially with suppurative thrombophlebitis, ligation of the vein well above the lesion may be indicated in an attempt to prevent extension. This was first performed by Hunter in 1784.³⁵ Many have since advocated this procedure by a variety of techniques, some of which include excision of a portion of the vein. The most frequent site of this operation is the femoral vein just peripheral to the junction with the deep femoral vein. One object of the procedure is the prevention of embolism, but we know of two patients with pulmonary emboli shortly after the ligation. It is thus no guarantee against embolism. Two possibilities suggest themselves. Either the wall of the vein was inflamed above the ligation so that another thrombus started above the ligation (we know that this can happen) or another unknown vein was involved with thrombophlebitis. Both of the above mentioned patients had received sympathetic blocks prior to the ligation.

Ligation and retrograde injection, especially by the technique described by Pratt³⁶ constitutes a definite advance in the treatment of varicosities, but it is doubtful whether this technique should be applied if there is any evidence of active inflammation. In this Pratt concurs.

Incision and drainage is very rarely advisable and should be restricted to frankly suppurative cases. Thrombectomy has been advocated by certain workers^{37, 38} since the time of Demons³⁹ (1881), on the basis that it

reduces the incidence of pulmonary emboli and the tendency to reflex vasospasm Kulenkampff⁴⁰ recently reported sixty-one cases advocating that after removal of the thrombus the vein should be ligated proximally. The risk of emboli would obviously be reduced by performing the ligation first and then there would be doubt of the value of the thrombectomy.

SUMMARY

In summary, an attempt has been made to survey the present status of knowledge and theory regarding thrombophlebitis. The next few years should produce marked advancement in our understanding of this problem and will undoubtedly revise many of our present conceptions.

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NEWER KNOWLEDGE OF BLOOD TRANSFUSIONS*

JOHN SCUDDER, CHARLES R. DREW, ELIZABETH TUTHILL, B.Sc.,
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ABEL¹ in 1914 reported on combating experimental hemorrhagic shock in dogs by infusing red cells suspended in Locke's solution after discarding the plasma. Subsequently, Rous and Turner² demonstrated that the longevity of the red blood cells could be enhanced if such erythrocytes were kept in a dextrose-citrate solution in a refrigerator. These two experimental observations led Robertson³ to use preserved red cells in treating the wounded at the casualty clearing stations of the Third Army of the B. E. F. during the first World War. Twenty-two such red cell transfusions, some fortified with gelatin, were given to twenty individuals. Of these, eleven were discharged to the base hospital and nine died. Among the latter, all except one were temporarily benefited by the stimulating effect of the cells.

Perry⁴ extended the preservation of erythrocytes by showing that the oxygen-carrying power of the red blood cells was maintained better in a solution of dextrose and lithium citrate than in one containing sodium citrate. Cells so preserved were transfused to man after removing the supernatant plasma.

Prior to this use of preserved cells, Richard Weil,⁵ in 1915, had transfused citrated human blood which had been kept for several days in cold storage.

The observations of Yudin⁶ on the transfusion of stored cadaver blood and the experimental wide scale use by Durán Jordá⁷⁻¹⁰ of conserved citrated blood during the Spanish Civil War stimulated investigations in many laboratories.^{17, 18, 19}

In the present war, plasma or serum is being used in preference to both red cell and preserved blood transfusions.

What has led to this complete reversal in current medical thought?

* Presented before The New York Academy of Medicine January 17, 1941, in the Friday Afternoon Lecture Series. This study was made possible by a grant from the Blood Transfusion Betterment Association, New York, New York. From the Surgical Pathology Laboratory of the College of Physicians and Surgeons, Columbia University, New York, New York.

TABLE I
CHANGES IN CELLULAR ELEMENTS OF PRESERVED BLOOD

Over 30 days in refrigerator at 4-6° C

<i>Constituent</i>	<i>Heparin²²</i>	<i>Sodium citrate²³</i>
Red Blood cells	Cell counts at constant level for a month	Moderate destruction of erythrocytes after 15th day with decrease of 1,000,000 to 1,500,000 at end of 30 days
Mean cell diameter (Halometer method)	20 per cent decrease in 30 days	
Hemoglobin (Hellige)	Total remains constant 15-25% in plasma in 30 days	Total remains constant 15-25% may diffuse out in 30 days
White blood count	50% decrease in 24 hours	Fall 27% in first 5 days
Polymorphonuclear neutrophiles	Show earliest and most rapid degenerative changes with nuclei losing shape 50% decrease in 48°	Nuclear changes in 24 hours In 48 hrs 50% decrease In 15 days liquefaction and droplet formation becoming subsequent smudges
Eosinophiles	Show least changes in size, shape and staining qualities over 1 month	Well preserved at end of 30 days
Basophiles		Well preserved at end of 30 days
Lymphocytes	Retain shape, size and staining properties better than neutrophiles Recognizable at end of 30 days	More resistant than polymorphonuclears Recognizable at end of 30 days
Monocytes	More resistant than neutrophiles	Difficult to trace
Thrombocytes	Rapid decrease during first 3 days	Early decrease

CONDITIONS OF EXPERIMENT

Donor	Type O	Type O
Blood (venous)	50 cc	45 cc
Anticoagulant	5 mg dry heparin (Connaught)	0.5 cc 35% sodium citrate solution
Test tube	Round bottom—Internal diameter 11 cm	Flat bottom—Internal diameter 16 cm
Mixing of sample	0.5 cc plasma removed for analysis after centrifugation 1 hr 3000 RPM Blood mixed inverting tube 15 x	Shaking
Time of experiment	Fall, 1938	Winter, 1939

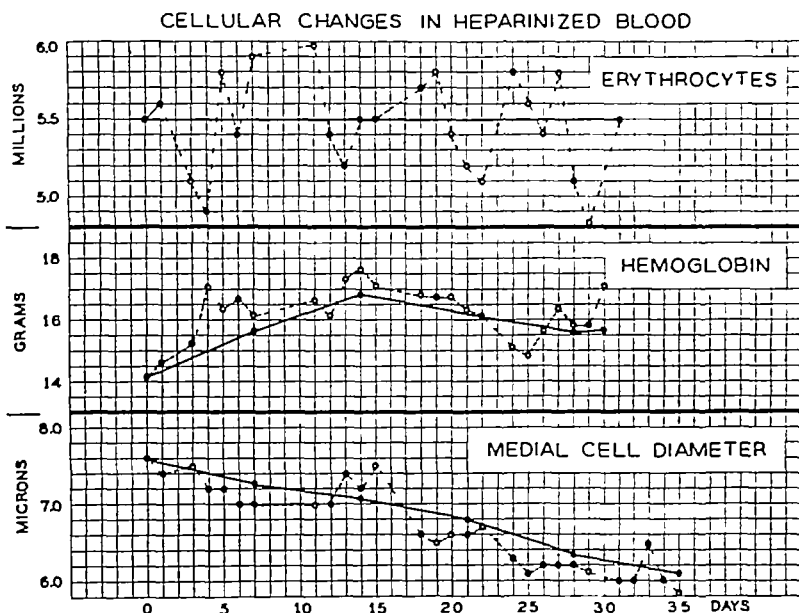


Figure 1

The answer lies in the fact that blood on leaving the vascular system starts to undergo degeneration immediately²⁰ To appreciate what some of these changes are, will enable one to use those measures which will hinder or retard them, thereby prolonging the usefulness of preserved blood

The following report deals only with the work done in our laboratory It will be treated under three separate heads

- 1 Changes which occur in the cellular elements of the blood
- 2 Changes which occur in the electrolyte distribution
- 3 Changes which appear in the protein patterns*

CHANGES IN THE CELLULAR ELEMENTS

Methods Two sets of experiments were carried out Equal amounts of freely flowing venous blood were collected in each of thirty-five sterile test tubes The first used dried heparin (Connaught), the second used sodium citrate solution as anticoagulant The results are tabulated in Table I and a few of the changes are illustrated in Figs 1-5^{22 23}

It is apparent that changes take place with both anticoagulants The neutrophilic leukocytes show the earliest alterations

* These were carried out under D. A. MacInnes of the Rockefeller Institute for Medical Research

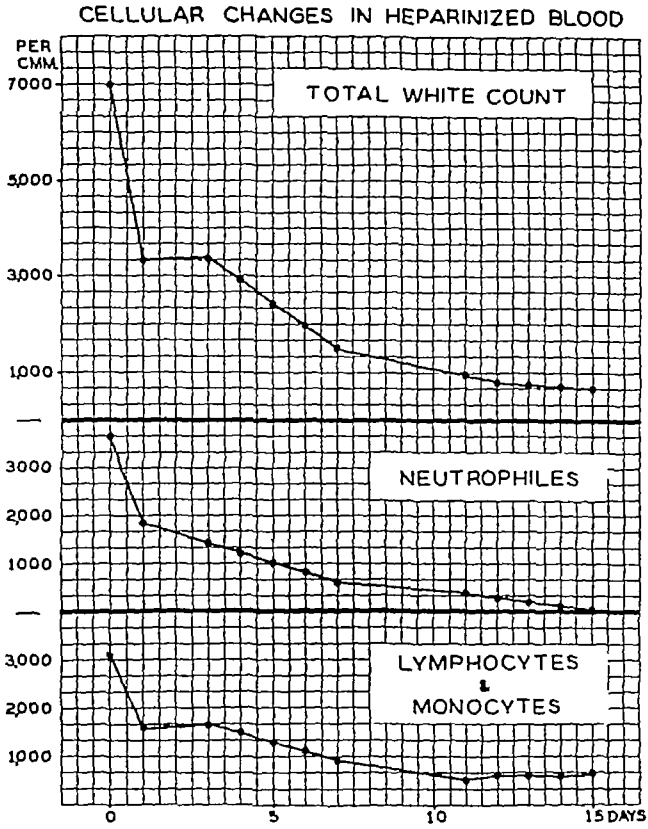


Figure 2

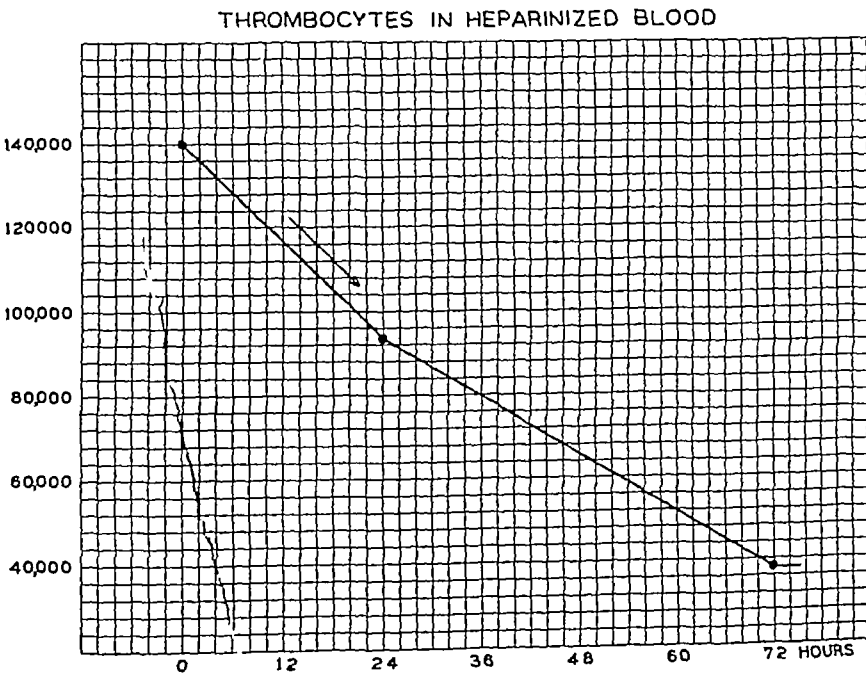


Figure 3

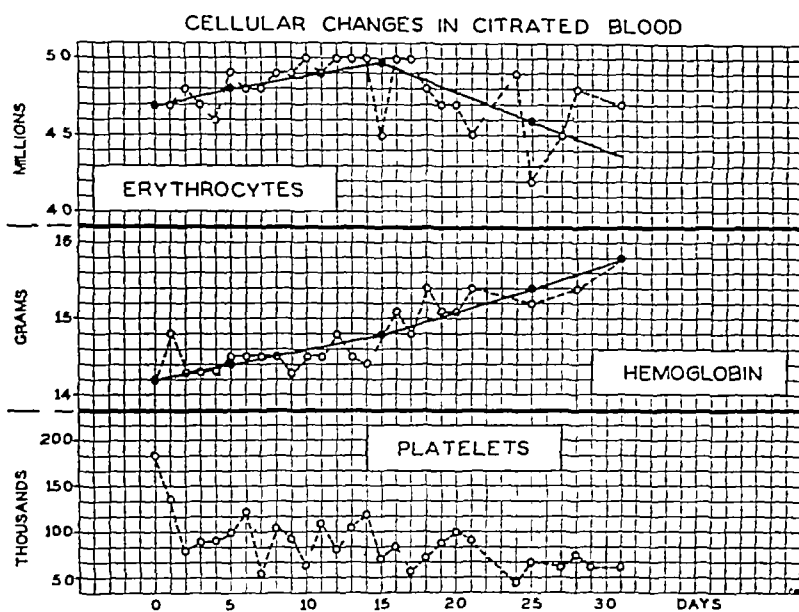


Figure 4

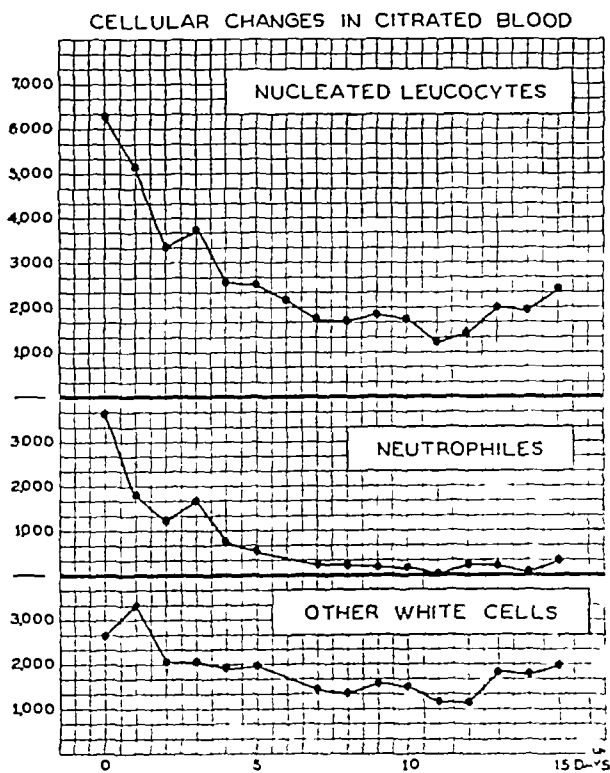


Figure 5

CHANGES IN ELECTROLYTE DISTRIBUTION

The Permeability of Erythrocytes to Sodium and Potassium The exit of the potassium ion from certain plant cells is one criterion of the permeability, for the integrity of the cell is unlikely to be maintained under adverse conditions on account of the steep concentration gradient which exists between the intracellular potassium and that of the external solution ²⁴⁻²⁷

Gurber²⁸ reported the impermeability of erythrocytes to sodium and potassium, but Hamburger and Bubanovic²⁹ pointed out in 1910 that if the salt concentration of the serum is changed, or the carbon dioxide tension altered, both cations will readily cross the cell membranes

In vivo, disturbances in both the plasma potassium and sodium ion concentrations occur ^{30, 31, 32, 33, 34, 35}

In vitro, a rapid diffusion of the potassium ion from the erythrocytes into plasma transpires ^{17, 36, 37, 38, 39} With this, there is an associated lowering of the sodium ion ^{10, 40, 41}

These changes were reinvestigated with the hope of ascertaining some underlying mechanism

Analytical Procedure Sodium was precipitated as uranyl zinc sodium acetate according to the method of Butler and Tuthill ⁴² Potassium by a modification of the argenticobaltinitrite method ^{33, 34, 43, 44} Ammonia nitrogen by the isothermal distillation method of Conway ^{20, 45}

Preliminary Analyses Similar quantities of venous blood were collected from the same donor in three separate hematocrit tubes In the first, there was no anticoagulant In the second, there was placed exactly 1 milligram of sodium heparin In the third, 0.5 cc of 3.5 per cent sodium citrate solution was mixed with exactly 4.5 cc of blood

RESULTS OF PRELIMINARY ANALYSES FOR SODIUM

1	Serum sodium	321.7 mg %	139.8 M eq/L
2	Heparinized plasma sodium*	317.9 mg %	138.1 M eq/L
3	Citrated plasma sodium*	328.9 mg %	142.8 M eq/L

* Corrected for sodium in anticoagulant

Next, an attempt was made to establish a series of normal values, using each of the anticoagulants

Experiment 1 Blood samples were collected from each of eight normal individuals into hematocrit tubes with an internal diameter varying between 6 and 7mm and containing exactly 1 milligram of the sodium

TABLE II

PLASMA SODIUM IN NORMAL HEPARINIZED BLOODS

Corrected for Sodium in Anticoagulant

<i>Number</i>	<i>Milligrams Per Cent</i>	<i>Milliequivalents Per Liter</i>
1	320.1	139.2
2	319.9	139.1
3	323.4	140.6
4	316.0	137.4
5	316.7	137.7
6	322.0	140.0
7	317.9	138.2
8	317.9	138.2
	319.2	138.8

TABLE III

PLASMA SODIUM IN NORMAL CITRATED BLOODS

Corrected for Sodium Added

<i>Number</i>	<i>Milligrams Per Cent</i>	<i>Milliequivalents Per Liter</i>
1	317.3	138.0
2	318.0	138.3
3	337.8	146.9
4	316.8	137.8
5	315.5	137.2
6	309.8	134.7
	319.2	138.8

salt of heparin. The results of the plasma sodium analyses are recorded in Table II. These compare closely with the accepted values.

Experiment 2 In a manner similar to Experiment 1, the range of normal values was checked on citrated blood plasma. The results are listed in Table III.

TABLE IV

A COMPARISON OF THE RATE OF CHANGE IN THE PLASMA OF PRESERVED BLOOD OF AMMONIA, SODIUM, AND POTASSIUM ION CONCENTRATION

Serial Number	Initial Donor	Age of Blood in Hours	Ammonia—Nitrogen		Sodium		Potassium	
			Mg Per Cent	M eq/L	Mg Per Cent	M eq/L	Mg Per Cent	M eq/L
504	A	15	0.31	0.21	2.995	130.2	31.2	8.0
584	J	15	0.28	0.20	3.13.9	136.5	37.5	9.6
555	P	16	0.41	0.29	3.17.2	137.9	30.9	7.9
502	A	16	0.32	0.23	3.17.7	138.1	21.5	5.5
586	Y	18	0.19	0.35	3.14.8	136.9	34.0	8.7
532	B	18	0.46	0.33	3.05.2	132.7	32.6	8.3
507	B	19	0.49	0.35	3.20.7	139.4	32.6	8.3
509	N	20	0.30	0.21	3.19.2	138.8	27.4	7.0
533	J	38	0.57	0.41	2.97.8	129.5	34.0	8.7
512	C	68	0.87	0.62	2.83.5	123.3	55.5	14.2
484	P	69	1.05	0.75			83.7	21.4
592	W	93	1.08	0.77	2.61.0	113.5	133.0	34.1
541	L	116	0.99	0.71	2.85.6	124.2	132.0	33.8
557	K	140	0.92	0.66	2.51.9	109.5	95.8	24.5
483	II	140	1.06	0.76			123.0	31.5
531	Y	163	1.15	0.82	2.56.7	111.6	126.0	32.2
611	L	163	0.81	0.58	2.50.1	108.7	136.0	34.8
549	W	184	1.09	0.78	2.60.4	113.2	142.0	36.3
593	P	209	1.00	0.71	2.51.2	109.2	135.0	34.5

Experiment 3 Uniform samples of blood were obtained from each of nineteen flasks at the time of giving the preserved blood transfusions. After centrifuging, the plasma was analyzed for its ammonia, potassium, and sodium content. The corrected results are tabulated in Table IV.

Stored blood loses potassium at a constant rate from the cells. The extreme values recorded show a decrease of 30.7 milliequivalents for plasma sodium during the first week. Sodium, therefore, enters the red blood cells rapidly during the first five days and then approaches at a steady state. During the same period, there is an increase of 29.3 milliequivalents of potassium.⁴⁶ With these changes, ammonia nitrogen had increased to 0.58 milliequivalents per liter.

A possible explanation may lie in the work of Jacques⁴⁷ who demonstrated that changes in ammonia concentration alter the permeability of the sea algae, *Valonia macrophysa* Kütz, to both sodium and potassium.^{24, 27}

Conway^{20, 45} saw a sharp rise in ammonia concentration occur within the first few minutes after the shedding of blood, this was slowed by collecting blood under CO₂.

The permeability of the erythrocyte protoplasm to cations has been widely investigated.^{29, 48, 60} Certain factors, however, such as an increase in CO₂ tension⁴¹ or change in fluid medium,⁶¹ or change in pH⁶² will markedly alter this state of "selective permeability."

Maizels⁶¹ in 1935 indicated that moderate shifts in pH do not alter the permeability of erythrocytes in respect to sodium and potassium, pronounced changes do affect the permeability, however.

It has been noticed that among the different preservatives used in blood storage, the one containing glucose and salt in the proportions suggested by Rous and Turner² prevented hemolysis but did not alter the outward diffusion of potassium.³⁰ The pH of the plasma which had been preserved with Rous' solution was 7.1. Others, reporting their results on blood stored in glucose, record a fall in the pH of such specimens.

Sheep's blood preserved with and without CO₂ revealed marked differences in both hydrogen and ammonia ion concentrations.³³

To test again the effect of CO₂ on human blood, the following controlled observations were made:

In each of the eight experiments, blood was obtained in the usual manner from a different individual, isotonic solution of sodium citrate being used as the anticoagulant. One half of the sample was drawn into

TABLE V

EFFECT OF CARBON DIOXIDE ON SODIUM, POTASSIUM, AMMONIA-NITROGEN, AND pH CHANGES
IN THE PLASMA OF PRESERVED BLOOD

Date	NH ₃ -N						Na				K				pH			
	Ur		CO ₂		Mg %	M eq /L	Air		CO ₂		Mg %	M eq /L	Air		Mg %	M eq /L	Air	CO ₂
	Mg %	M eq /L	Mg %	M eq /L			Mg %	M eq /L	Mg %	M eq /L								
9/11/39	0.10	0.07	0.01	0.01	322.1	140.1	337.4	146.7	17.1	4.4	17.4	1.5						
9/12/39	0.37	0.26	0.08	0.06	324.0	140.9	336.0	146.1	31.3	8.0	25.4	6.5					7.76	7.18
9/16/39	0.55	0.39	0.18	0.13	302.6	131.6	333.0	144.7	56.4	14.4	34.6	8.8					7.58	7.22
9/19/39	0.77	0.55	0.30	0.21	296.4	128.9	317.0	137.8	73.9	18.9	49.9	12.8					7.65	7.31
9/26/39	0.94	0.67	0.44	0.31	276.8	120.4	312.5	135.9	91.6	23.4	62.1	15.9					7.69	7.17

an atmosphere of carbon dioxide while the control was collected in air. The details of the experiment have been previously reported.⁴¹

Results The results of one of these experiments in which determinations of the concentrations of ammonia, sodium, and potassium ions were made at intervals during a two-week period is recorded in Table V. It is noted that the concentration of the ammonia ion in the blood taken under carbon dioxide was lower, the rates of potassium and sodium changes slower, and the pH nearer neutral at the end of the experiment.

The concentration of ammonia ion in the control, beginning at 0.07 milliequivalents per liter, rose to 0.67, in the CO₂ environment, it began at 0.01 and rose to 0.31. The increase in the concentration of ammonia ion for the two-week period in the blood taken in CO₂ is, therefore, only 50 per cent of the increase noted in blood taken in air. Plasma sodium values decreased in the control 19.7 milliequivalents per liter, in CO₂, 10.8. Plasma potassium values increased in the control 19.0 milliequivalents per liter, in CO₂, 11.4.

The plasma pH value in CO₂ approached the normal more closely than did the samples taken in air. Hemolysis in the latter was greater than in blood collected in carbon dioxide.

CONCLUSIONS

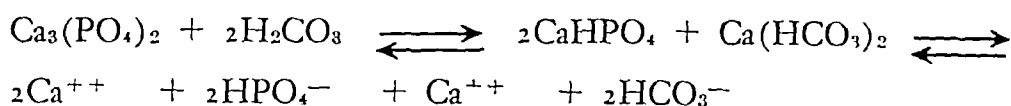
1. There is a rapid, constant decrease in sodium in the plasma of preserved blood.
2. This decrease is roughly inversely proportional to the increase in plasma potassium.
3. There is a suggestive evidence that with an increase in ammonia content of blood plasma, permeability of the erythrocyte protoplasm to these two ions is changed.
4. Blood drawn under carbon dioxide maintains a plasma pH value nearer neutral than blood drawn in air.
5. Changes in the plasma concentrations of ammonia, sodium, and potassium ions in such blood collected in CO₂ is less than in air.
6. Hemolysis is retarded by collecting blood in an atmosphere of carbon dioxide.

CHANGES IN CALCIUM, MAGNESIUM AND PHOSPHORUS CONTENT

Of the six minerals commonly present in living matter calcium has the greatest tendency to form insoluble salts.⁴² In man it occurs in the form

of the phosphate or carbonate and may be divided into two forms diffusible and indiffusible. The former is capable of existing in the ionized state and only a small portion is ever actually dissociated from its very stable salts⁶⁴

In the body it exists as tricalcium phosphate, a relatively insoluble compound, but under the influence of carbonic acid of the plasma, it is partly converted to the more soluble calcium bicarbonate and calcium hydrogen phosphate



Methods Calcium was determined by the method of Clark and Collip,⁶⁵ the final titration being done against a standard sodium oxalate solution

Phosphorus, determined as phosphate, was done by an adaptation of the methods of Clark and Collip⁶⁵ and Fiske and Subbarow.⁶⁶ Following the suggestion of Gamble⁶⁷ the base equivalence is 1.8 times the molecular concentration of HPO_4 . An adaption of several methods^{65, 66, 68} was used in determining magnesium

Procedure From a voluntary donor, 450 cc of blood was drawn in air into a bottle containing 50 cc of 3.5 per cent sodium citrate solution, and then divided into twelve equal portions and kept in a refrigerator. On the plasma of one sample, calcium, magnesium, and phosphorus analyses were done on the day of collection and on the following day. Then, on every second day, two tubes were taken. From one, the plasma was immediately removed, from the other, only after inverting five times and centrifuging for thirty minutes.

Results The results are presented in Table VI and Table VII and indicate the changes which took place during nine days. Each is an average of at least two separate determinations by two individuals.

Discussion Joseph and Meltzer⁶⁹ reported in 1910 that the toxicity of the chlorides of magnesium, calcium, potassium, and sodium varied in almost inverse proportion to the quantities found in blood, particularly in the plasma. Since plasma potassium concentration is greater than plasma magnesium concentration, significant increases in the latter, according to this theory, would be more toxic. These results indicate that during the nine day observation period, there is very little outward diffusion of magnesium.

TABLE VI

PLASMA CALCIUM AND PHOSPHORUS CHANGES IN PRESERVED BLOOD

Age in Days	Calcium				Phosphorus			
	Before Shaking		After Shaking		Before Shaking		After Shaking	
	Mg %	M eq/L	Mg %	M eq/L	Mg %	M eq/L	Mg %	M eq/L
0	92	46			36	21		
1	88	44	87	44	35	20	34	197
3	89	45	87	44	34	197	34	197
5	86	43	92	46	35	20	36	21
7	87	44	87	44	38	22	36	21
9	91	46	91	46	37	21	40	23

TABLE VII

PLASMA MAGNESIUM CHANGES IN PRESERVED BLOOD

Age in Days	Magnesium in Milliequivalents per Liter	
	Before Shaking	After Shaking
0	23	
1	23	235
3	25	24
5	26	24
7	25	25
9	24	24

SUMMARY

1 The plasma calcium ion concentration of preserved blood remains constant for a period of nine days and is not increased by shaking

2 There is no definite increase in the plasma phosphorus content. This is not accentuated by shaking even in the nine-day old blood

3 Magnesium diffuses out of the erythrocytes of stored blood at a very slow rate if at all. Shaking apparently does not increase this

4 The actual increase in magnesium at the end of nine days' storage appears to be too small to account for any toxic manifestation following transfusions of such preserved bloods

TABLE VIII
ACID-BASE COMPOSITION OF FRESH BLOOD PLASMA

<i>(Expressed in Miliequivalents per Liter)</i>					
<i>Base</i>			<i>Acid</i>		
<i>Ion</i>	<i>Gamble</i>	<i>Gutman</i>	<i>Ion</i>	<i>Gamble</i>	<i>Gutman</i>
Na'	142	142	HCO ₂ '	27	28
K'	5	5	Cl'	103	104
Ca''	5	5	HPO ₄ ''	2	2
Mg''	3	2	SO ₄ ''	1	1
			Org Ac	6	1
			Protein	16	18
Total	155	154		155	154

CHANGES IN THE TOTAL ELECTROLYTE STRUCTURE OF THE PLASMA OF PRESERVED BLOOD

With these observed alterations in the potassium, sodium, ammonia, calcium, phosphorus, magnesium, and hydrogen ion concentrations, the status of total ionic balance in aging blood needs investigation

To this end, freshly drawn blood was set aside at approximately monthly intervals for four months. The cations were determined as in the previous section, and of the anions, the bicarbonate, chloride, phosphate, and hydrogen ions were analyzed. The sulphates, organic acids, and proteins were omitted, as there is not a complete unanimity of opinion concerning the equivalent values to be assigned to the organic acid and protein components on the acid side of the equation.

The chlorides were determined by the method of Van Slyke⁷⁰ and the carbon dioxide and oxygen by the method of Van Slyke and Neill.⁷¹ The pH measurements were carried out by means of the glass electrode potentiometric method of MacInnes and Longworth.⁷² The bloods which were examined on the fifth, sixty-eighth, and one hundred seven-teenth days of preservation had been stored in narrow-waisted dumb-bell-shaped flasks which contained 50 cc of 3.5 per cent sodium citrate and 450 cc of blood. The interface diameter between the settled cells

TABLE IX

CHANGES IN TOTAL CATION STRUCTURE
IN THE PLASMA OF PRESERVED BLOOD

(Expressed in Miliequivalents per Liter)

Cations	Normal Gutman	Age in Days					
		5	21***	68†	93*	117†	117**†
Na'	142	122.4	106.3	119.0	89.7	105.2	120.7
K'	5	28.2	35.0	29.2	54.2	40.6	28.8
Ca''	5	5.3	5.5	5.7	5.7	5.3	5.4
Mg''	2	1.9	2.5	2.2	2.4	2.7	2.1
Total	154	157.8	149.3	156.1	152.0	153.8	157.0

CHANGES IN ANION COMPOSITION IN
THE PLASMA OF PRESERVED BLOOD††

Anions

HCO ₃ '	27	16.6	11.9	15.4	12.4	10.7	16.5
Cl'	103	99.3	99.7	100.5	80.0	99.7	107.0
HP ₂ O ₄ ''	2	1.9	6.0	5.2	8.2	7.5	3.4

* Commercial bottle
Interface 10.4 cm** Undisturbed plasma
† Interface 3.5 cm*** Wide mouth flask
Interface 8.6 cm

and plasma was 3.5 cm. All but one of these flasks were inverted to mix thoroughly the cells and plasma, before the sample was centrifuged and the plasma removed for analyses. The values in the last column were obtained from the plasma of a blood one hundred seventeen days old, which had not been disturbed during the entire period. The twenty-one day old blood was kept in a wide-mouthed flask (interface 8.6 cm) while the ninety-three day old blood (column six from the left) was collected in a commercial bottle (interface 10.4 cm) which contained 70 cc of 2.5 per cent sodium citrate in physiologic saline under vacuum of 24-26 inches of mercury. All values are corrected for dilution and added sodium or chloride.

Discussion The greatest changes are seen in the sodium and potassium ion concentration, particularly in the bottle in which the blood

†† We are indebted to A. B. and E. B. Gutman for permission to use their figures for normal human serum.

was collected under vacuum

Calcium in these bloods stored for longer periods, acted similarly to that in bloods stored for shorter periods and showed relatively little change, nor did mixing a one hundred seventeen day old blood increase the plasma calcium content

Magnesium, as the second largest constituent of the cells, might have been expected to show a greater outward diffusion

The total average number of milliequivalents in the six bloods amounts to 154.3 compared with the control normal value of 154.0

The alkali reserve of the plasma as measured by the CO_2 combining power decreases with age. The chloride ion concentration decreases, but not to the extent of the sodium ion. The plasma chloride concentration of the blood which had been collected in a commercial vacuum bottle and which contained an additional 70 cc. of normal saline was strikingly low when compared with the high chloride values in the samples taken under atmospheric pressure without the addition of saline.

The plasma phosphate concentration gradually increases in the blood with increasing age, but never as great as that of potassium.

The pH of stored blood after mixing with the plasma varied between 7.1 and 7.34.

The quantity of the determined anions in these six bloods ranged from 100.6 to 126.9 milliequivalents per liter, with an average of approximately 117. These figures are exclusive of the sulphate, protein and organic acid anions.

Summary In the plasma of bloods stored in an electric refrigerator thermostated at 4°C for a period ranging from five days to four months, the following changes were observed

- 1 Potassium increases
- 2 Sodium decreases
- 3 Calcium remains practically constant
- 4 Magnesium shows little change
- 5 Bicarbonate decreases
- 6 Phosphate increases, particularly following agitation
- 7 Chlorides decrease in plasma intimately mixed with the cells remain constant or slightly increased when left undisturbed
- 8 The total cation concentration remains constant, despite great variations in the plasma content of individual cations
- 9 The observed loss of determined anions suggested that balance

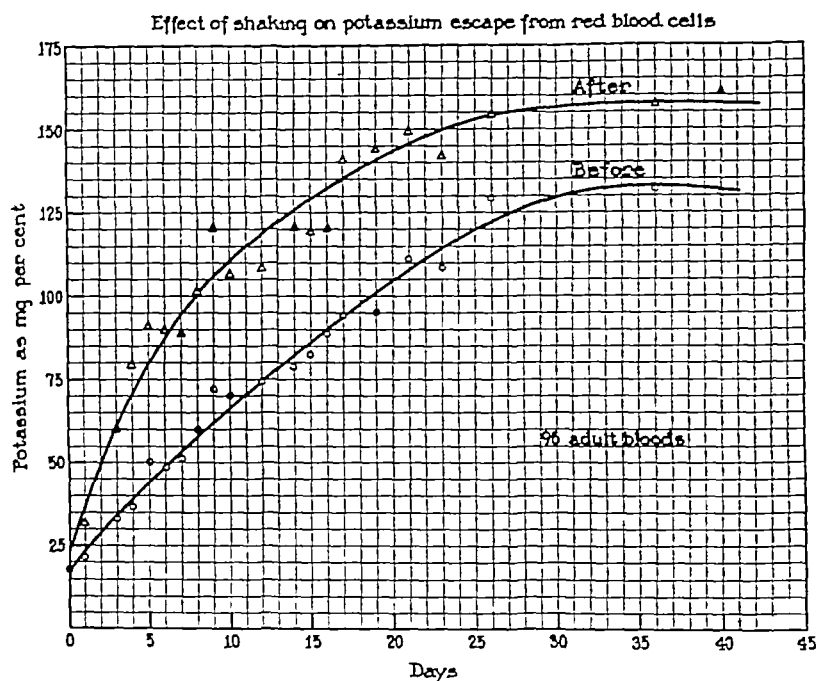


Figure 6

is maintained by a gradual increase in the organic acid ion component and a decrease in albumen

- 10 The pH changes of the whole blood after mixing are slight

SOME FACTORS GOVERNING TRANSPORT OF BLOOD

In a previous report trauma to blood in the form of shaking caused loss of potassium from the cells and rapid laking³⁹

During the winter of 1938-1939, the blood from ninety-six voluntary donors at the Mt Sinai Hospital* was collected in mason jars containing 25 or 30 per cent sodium citrate. From these, five to six cubic centimeters were removed and stored in identically shaped centrifuge tubes. These tubes were transported at once to the Presbyterian Hospital, a distance of six miles.

There was no gross hemolysis in these tubes containing freshly shed blood, whereas old blood transported at the same time in partially filled mason jars revealed striking hemolysis.

At varying intervals, the blood was removed from the refrigerator and mixed by inverting the tube 20 times. The results are depicted in Fig. 6.

* We express our gratitude to N. Rosenthal and his staff for their coöperation in this investigation and to the Mt Sinai Hospital for permission.

TABLE X

INCREASING EFFECT OF TRAUMA WITH INCREASING AGE OF BLOOD

Time in Weeks	Plasma Potassium				Plasma Ammonia Nitrogen			
	as Milligrams Per Cent		as Milliequivalents Per Liter		as Milligrams Per Cent		as Milliequivalents Per Liter	
	Before	After	Before	After	Before	After	Before	After
0	25.4	26.0	6.5	6.7	0.09	0.151	0.064	0.11
1	63.1	149.2	16.1	38.2	0.58	0.126	0.41	0.90
2	73.6	172.6	18.8	44.1	0.87*	1.45*	0.62	1.04

* Volume of blood, 25 cc

All other experiments, volume of blood 50 cc

Discussion The curve representing the diffusion of potassium in the unshaken blood is the same order of magnitude as previously reported for citrated blood³⁰ In each instance, agitation caused both potassium and hemoglobin to leave the cells. During the first few days, this was not as great as later. As the plasma potassium concentration approached that within the cells (i.e., decrease in concentration gradient) shaking dislodged less.

To check these findings a controlled experiment was set up.

Method The blood of two voluntary donors, type A and type B, was drawn at weekly intervals and placed in 50 cc colorimeter tubes with an internal diameter of 2 cm containing 5 cc of 3.5 per cent sodium citrate solution.

At the end of two weeks following the drawing of the last blood, the previously drawn samples were removed from the refrigerator where they had been kept, stoppered and sealed, at a temperature of 5 to 6° C.

A small sample of the plasma was taken from each of the six tubes for potassium and ammonia determinations. After this, all of the tubes were rotated end over end on a specially devised piece of apparatus for twenty minutes, centrifuged, and from each, samples were taken for potassium and ammonia determinations after the rotating.

The diffusion of potassium from red blood cells to plasma following trauma increases rapidly with increasing age of the blood. This suggests that if transportation of blood is contemplated, it should be done while the blood is fresh for the damage incurred by the cells is less at this time than when the blood is older.

The effects of shaking can be greatly reduced by filling the container completely with blood. Durán Jordá¹⁰ employed this principle during the recent Spanish Civil War in which preserved blood was used on an extensive scale.

It would appear, then, that in the transportation of preserved blood, factors which would minimize the loss of intracellular substances, such as decreasing the interface between cells and plasma, obviating any interface between liquid and gas by filling the container completely, should be also considered in addition to proper refrigeration, etc.

Summary 1 The diffusion of intracellular substances (potassium and hemoglobin) is accelerated by shaking and factors which limit this should be employed in blood preservation.

2 Transportation of preserved blood adequately refrigerated in suitable containers completely filled should be done early after shedding.

PLASMA

These studies indicate that degenerative changes occur as soon as blood leaves the vascular system, and progress with age. The large changes in the electrolyte composition might indicate its unsuitableness in those pathological states which are known to be associated with disturbances in the mineral metabolism, such as dehydration,^{32,33} adrenal insufficiency,^{31,34} and traumatic and hemorrhagic shock.^{33,35} Should large amounts of old blood be given rapidly in these conditions, dangerous sequelae might ensue.

Since the work of Bowditch⁷³ in 1871, increasing attention has been directed to both serum and plasma as possible substitutes for whole blood transfusion.^{21,74,75}

Amberson⁷⁶ in his review on this subject has pointed out some of the advantages of plasma.

Using the electrophoretic method of Tiselius,⁷⁷ as modified by Longworth,⁷⁸⁻⁸⁰ the stability of the various protein components in plasma has been investigated.⁻¹ These observations confirmed the previous work of Knoll⁸¹ who reported a decrease in albumin, a change in the albumin-globulin ratio, and an increase in gamma globulin.

To ascertain more exactly the magnitude of these alterations, blood was drawn from a single donor at varying intervals, and the plasma separated from the cells on the same day.

These values indicate a decrease in the albumin and a shift in the

TABLE XI
ELECTROPHORETIC PATTERN OF PLASMA FROM SAME INDIVIDUAL²¹

TYPE A													
Age of Blood Days	Composition						Mobilities, $U \times 10^{-5}$						
	Albumin per Cent	A/G	α/A	β/A	ϕ/A	γ/A	pH	Albumin	Globulin				Remarks
									α	β	ϕ	γ	
1 fresh	3.96	2.27	0.08	0.18	0.08	0.18	7.72	5.95	1.2	2.9	1.6	0.2	Citrate
12	3.81	1.92	0.11	0.21	0.07	0.20	7.71	6.15	1.3	2.9	1.6	0.1	Citrate
20	3.66	1.72	0.11	0.21	0.09	0.26	7.73	6.25	1.6	3.2	1.7	0.2	Citrate
28	2.89	1.51	0.12	0.27	0.08	0.26	7.75	6.18	4.5	3.1	1.7	0.3	Citrate

CONDITIONS OF EXPERIMENT

In brief, a four times diluted portion of plasma is dialyzed in a bag made from cellophane tubing constructed in such a manner as to give a large surface to volume relationship. The buffer with a pH at 7.8 to 25° C consisting of 0.025 M lithium diethyl barbiturate, 0.025 M diethyl barbituric acid, and 0.025 M lithium chloride is used. The dialysis is carried out from 18 to 72 hours in a two liter flask containing fresh buffer at a temperature between 0° and 2° C in a thermostatically controlled electric refrigerator. During the dialysis some precipitate separates out. It is, therefore, necessary to clear the protein solution in an angle centrifuge operated at 0° C before its introduction into the electrophoresis cell. The pH measurement is determined with the glass electrode of MacInnes and Longworth.²² The conductivity cell is of special design as well as the screened bridge used for the measurement of electrolytic conductance.²³ The establishment of a Donnan equilibrium is assumed when further dialysis produces no change in conductance of the protein solution and the outside solution has the conductance of the original buffer. The manner of obtaining the protein patterns²⁴ and of computing the different mobilities of the protein constituents has been published by Longworth, Sheelowsky, and MacInnes.²⁵

albumin-globulin ratio, accompanied by an increase in gamma globulin in the supernatant plasma of stored blood

In order to compare two common methods of desiccating plasma, blood was drawn from the same individual and the plasma of one portion was dried under vacuum from the frozen state, while the second portion was dried at body temperature as has been suggested by Edwards, Kay, and Davie⁸³ Electrophoretic patterns of the former gave a sharper picture than the one derived from the latter, indicating that the plasma reconstituted from the frozen state appears to be more normal²¹

Electrophoretic studies on liquid plasma preserved for five weeks, and in one instance for a year, showed evidence of some alterations particularly in the beta globulin region

PRACTICAL CONSIDERATIONS

Healthy donors, free from communicable diseases, are to be chosen Blood obtained from cadavers is to be rejected, both on account of marked electrolytic changes and degradation products^{21, 46}

In the collection of blood, strict surgical asepsis is to be observed *Cleansing the skin* is the most important step on account of the danger of contamination The skin of the antecubital fossa should be scrubbed with soap for two minutes This is removed with 70 per cent alcohol Three and a half per cent tincture of iodine is painted over the area and allowed to dry

Venipuncture Prior to the venipuncture, the skin is again swabbed with 70 per cent ethyl alcohol A wheal is raised over the selected vein by injecting 1 per cent novocain, in the center of which a small nick is made by using a number eleven blade A large needle of number thirteen or fifteen gauge is used for the phlebotomy

The blood is collected by the closed system This is superior to an open one for not only are chance contaminations decreased but also the loss of CO₂ is lessened The keeping qualities of blood are further enhanced by its collection in an atmosphere of carbon dioxide

As chemical changes are a function of temperature, the nearer zero the blood is stored, the slower will be these changes Freezing is to be avoided as it causes rupture of the red cells As chemical reactions are also a function of the surface area, it is natural that blood kept in specially designed bottles in which the interface between the plasma and the cells is small will enhance its keeping qualities

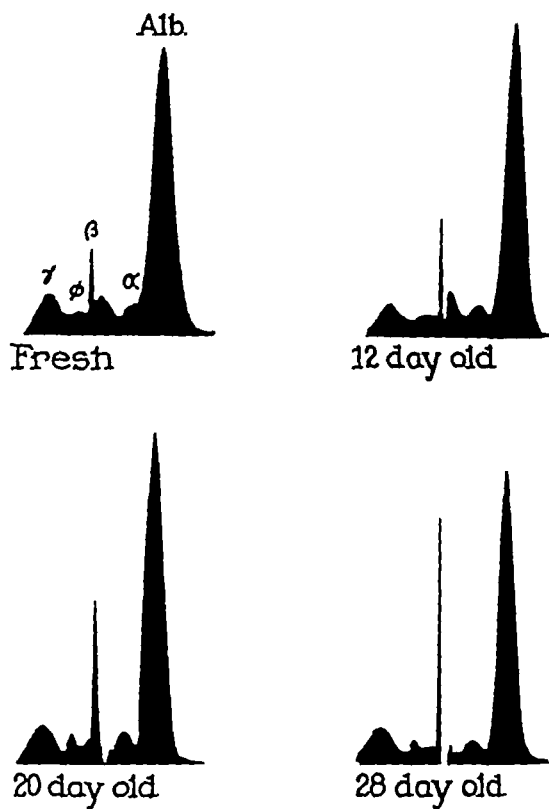


Figure 7—Electrophoretic patterns of preserved plasma from same donor. Four blood samples taken at different times, collected in 3.5 per cent sodium citrate and stored in four tubes in electric refrigerator at 4° C. Type A blood.

In the preparation of plasma, either the settling or the centrifuge method may be employed. With the latter, a bottle capable of containing the whole donation of blood (500 cc. in one bottle) is ideal for two reasons: 1) this halves the chance of contamination, and 2) the yield of plasma is greater. (Number three International General Electric centrifuge bottle—62 per cent citrated plasma yield vs. 46 per cent yield by settling seventy-two hours in a dumbbell shaped flask.)

In the removal of plasma, the procedure should be carried out in a dustproof, air-conditioned room, the air of which has been sterilized by ultraviolet light radiation. This will prevent possible airborne contaminants that have been found in plasma. The removal of the plasma should be carried out in a cabinet, thus minimizing further chance of infection.

Pooling and culture. The plasma from six to eight donor bottles is

siphoned off by suction and pooled in a two-liter flask. Cultures, both aerobic and anaerobic, are taken.

Final container The plasma is not considered suitable for final processing until a two-week negative report has been received. The pool is then broken down into the final containers, 500 cc of plasma may be mixed with 500 cc of saline. The last portion of the pool is collected in a pilot bottle so that the concentration of the plasma mixed with saline is similar to that of the larger bottles. This material serves as a test on the sterility of the final container as well as furnishing another check on the sterility of the plasma.

Filtration The safety of the plasma is enhanced if it has been passed through a clarifying and sterilizing filter. This step may be carried out after the initial pooling in a Seitz filter.

Dried Plasma As proteins are more stable in a dried state, the keeping qualities of the plasma may be enhanced if it is reduced to such a condition by a suitable lyophile process. The dried plasma can then be dispensed in glass sealed ampoules.

Use Dried plasma is turned into the liquid state by the addition of distilled water. It may be reconstituted in either an isotonic or hypertonic form, depending upon the amount of diluent added.

One abnormality, however, of such plasma is its extreme alkalinity.

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FREDERICK GRANT BANTING
1892-1941

IN MEMORIAM

SIR FREDERICK GRANT BANTING

The tragic death of Sir Frederick Grant Banting in an aeroplane accident in Newfoundland while on an important mission to England came as a profound shock to hundreds of thousands who are living to day only because of the brilliant researches of this benefactor of mankind. His death, while engaged in active service in line of duty," should be recorded as one of the major individual casualties of the present war. He was fifty years of age.

He is best known for his successful isolation of insulin, the internal secretion of the pancreas. This epoch making discovery was made in 1921 in his thirtieth year. The story of his success is a saga of individual determination, resourcefulness and singleness of purpose against overwhelming odds. Internationally famous professors with the facilities of well equipped laboratories at hand had been engaged unsuccessfully for two generations in an attempt to isolate the substance which controlled the concentration of glucose in the blood.

In the presence of such a record the ordinary person without equipment, money or special training would have abandoned the attempt to solve a problem which had resisted the efforts of so distinguished a group of scientists. But young Frederick Grant Banting was not an ordinary person. He was a young man possessed of an idea, a dreamer of dreams.

Such young men are capable of acting as powerful catalysts in the progress of the human race. Such was the effect of Banting's discovery of insulin. It aroused a new interest in the study of the glands of internal secretion which has revolutionized our conception of their function. And the end is not yet in sight.

The story of young Banting's life should be required reading for all young medical

students who begin their professional career without the benefit of wealth, influence or special training. He was born in 1891 in Alliston, Ontario, a typical Canadian small town. He received his elementary and high school education in that town. From Alliston he entered the University of Toronto where he received his M.D. degree. He began the practice of medicine, preferably surgery, in London, Ontario. To make out expenses he accepted a part time position as Assistant in Physiology at Western University, London, Ontario. Here he became interested in the internal secretion of the pancreas.

He read everything he could find on the early experimental work. Several men had barely missed isolating insulin. The preliminary work had been done in laboratories here and abroad. The necessary experimental data were in existence. All that was lacking was a mind steeped in the literature, engrossed with the problem and afire with an enthusiasm that would surmount all obstacles. Young Banting fitted ideally into this situation. In the fertile soil of his mind, prepared by weeks of study and thought, the existing facts assumed their proper relation to one another, and the synthesis occurred—a method for extracting the internal secretion of the pancreas.

The idea was born. The problem now was to apply the method. Would it work? This required elaborate laboratory equipment, experimental animals, trained assistants. How was a struggling practitioner, part-time clinical assistant, to obtain these? A lesser person would have been deterred by these formidable obstacles, but not Banting. It may be that he remembered that other young man who under similar circumstances was advised to go and "sell all that he had" in order to achieve his goal.

It may be recalled that the other young man failed to follow the advice, and was heard of no more. But to young Banting, the idea was more than wealth or possessions. He sold his office equipment, gave up his practice and entered upon the work that was to lead him to a knighthood bestowed upon him by his King.

As a direct consequence of this work, insulin is now available throughout the world for the control of diabetes and the saving of uncounted lives for normal and useful living. Also, as a result of this discovery, young Banting might have retained possession of his method and have become fabulously wealthy. But he was not tempted by riches. He desired to perfect the early crude insulin and to assure its availability to anyone, rich or poor, who needed it.

To this end his method of extraction was patented. All patent rights were then awarded to the University of Toronto. The University authorities created The Banting Research Foundation to receive all funds resulting from the sale of insulin. The following quotations are taken from the original announcement of the establishment of the Foundation:

"The purposes of the Banting Research Foundation have been specifically defined to be

- a To supplement the sum at present available, in the University of Toronto, for the support of the Banting and Best Chair of Medical Research.
- b To establish a fund for the adequate financial support of such scientific workers as may have proposed definite problems of medical research, and for whom funds are not available. Such assistance may be given

to persons working in the University of Toronto or elsewhere."

Dr Banting has received appropriate recognition from the Government of the Dominion of Canada (in the form of an annuity), from the Province of Ontario through the Governors of the University of Toronto (in the creation of the Banting and Best Chair of Medical Research, to which Dr Banting has been appointed) and in the award of the Nobel Prize in Medicine for 1928 (with Professor J. J. R. MacLeod).

Thus was created The Banting Research Foundation which is but "the lengthening shadow of a man." But Doctor Banting's greatest memorial will be the thousands of diabetics who survive because of his work.

Doctor Banting served in the Medical Corps in France in 1915-1919, and was wounded at Cambrai. Since 1923 he had served as Professor of Medical Research in the University of Toronto.

Although one of his outstanding traits was modesty, he was showered with honors such as few men at fifty years of age have achieved. He received the Nobel prize for distinguished scientific achievement in 1928. He was made a F.R.C.S. in 1930, F.R.S. in 1935, F.R.C.P. in 1936, D.Sc. (McGill) in 1939. He was knighted in 1934. The New York Academy of Medicine honored itself by conferring on Doctor Banting an Honorary Fellowship in 1938. He received many other honors from universities and distinguished scientific groups here and abroad. Truly it may be said of Sir Frederick Grant Banting: "He was a man, take him for all in all," we "shall not look upon his like again."

JAMES RALPH SCOTT

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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BULLETIN OF
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JUNE 1941

UTILIZATION OF SELECTIVE
MICROBIAL AGENTS IN THE STUDY
OF BIOLOGICAL PROBLEMS

Harvey Lecture, March 21, 1940

RENÉ J. DUBOS

Associate Member The Rockefeller Institute for Medical Research

ON THE third of August, 1857, Pasteur presented before the Scientific Society of Lille the first of his studies on the microbial theory of fermentation, "Mémoire sur la fermentation appelée lactique." On this occasion, he expressed his belief that, for each type of fermentation, one would find a specific ferment, characterized not only by its morphology and resistance to inhibitory substances, but also by its specific behavior as a chemical agent.¹

On December 21st of the same year, Pasteur announced, at the end of his memoir on alcoholic fermentation, that he had observed a new "mode of fermentation" which attacked the *d*-form of tartaric acid, but which was inactive against the *l*-form,² experimental details concerning this observation were presented on March 29, 1858,³ again in 1860 Pasteur described that a mold, *Penicillium glaucum*, exhibited the same specific behavior toward tartaric acid, attacking the *d*-form and not the *l*-form.⁴ He pointed out that this selective fermentation afforded an

easy technique for the separation of the *l*-tartaric acid from the racemic mixture, and that the method would probably be applicable to the separation of other isomers. He also emphasized that since "the character of dissymmetry of organic compounds can modify the chemical reactions of physiological order," the phenomenon of specificity which he had observed was probably of great biological significance.

The very beginnings of experimental microbiology thus demonstrated the specific character of the biochemical reactions induced by microorganisms, and suggested to biochemists and physiologists new techniques and new problems. It is hardly necessary to state that bacterial physiology has repeatedly confirmed Pasteur's views on the part played by microbial life in the economy of natural processes. If organic matter does not accumulate in nature, it is because countless species of microorganisms hydrolyze it, oxidize it and eventually break it down to carbon dioxide, ammonia, water, and mineral salts. We know furthermore that, under natural conditions, each one of these microbial species is adapted to the performance of a limited, well-defined biochemical task. One may illustrate this statement by recalling the discovery of bacteria whose sole source of energy is the oxidation of ammonia to nitrites, of others which oxidize nitrites to nitrates, of still others which convert elementary sulfur to sulfuric acid, etc. Several species of bacteria which readily decompose cellulose fail to attack cellobiose or glucose, there are microorganisms which oxidize hydrogen, methane, petroleum, phenol, formol, etc. In fact, it can be stated that one can find in nature, in soil or water for instance, microorganisms capable of performing almost every possible type of biochemical reaction, many of which are not known to take place in the animal or the plant kingdoms. In many cases, the catalysts responsible for these reactions have been extracted from the microbial cells, and have been found to exhibit a remarkable specificity. Because of their cellular origin, these catalysts are able to operate under physiological conditions (pH, temperature, etc.) and this property, together with their specificity, renders them ideal reagents for the analysis of biological problems.

It is apparent, therefore, that given enough time, patience, and skill, the bacteriologist can discover in nature microbial reagents adapted to the study of a great variety of biological problems. The few examples which will be considered in the following discussion have been investigated at the Hospital of the Rockefeller Institute, they have been se-

lected because, in each case, new bacterial species were isolated from soil and active catalysts prepared from cultures of these organisms, in an attempt to discover reagents useful in the study of clinical problems under investigation in our hospital. It is perhaps justifiable, therefore, to emphasize that the facts here reported are not chance findings, but are illustrations of a method which has a distinguished past in bacteriological chemistry and which deserves the consideration of physiologists and biochemists.

The decomposition of creatinine by bacterial enzymes In the course of studies on renal function, it became necessary to develop a method for the quantitative estimation of the very small amounts of creatinine present in blood. The identification and analysis of creatinine in tissues and biological fluids have chiefly depended on colorimetric methods which are so unspecific that many authors have denied the very presence of creatinine in the circulating blood.

It was in an attempt to develop analytical methods specific for creatinine that several species of bacteria capable of attacking this compound were isolated from soil.⁶ Two of these bacterial species have been studied with some care, when grown in the proper medium, they have yielded enzyme systems in the form of resting cells which are capable of decomposing creatinine in the absence of bacterial growth. These enzyme systems exhibit a remarkable specificity.

Table I illustrates the effect of the enzyme prepared from the "NC" culture upon a number of substances which give the Jaffe reaction (one of the color tests most commonly used to detect the presence of creatinine). It is clear that, of the Jaffe reactive compounds which were tested, only creatinine was rapidly decomposed. The addition of one methyl group to the creatinine molecule completely inhibited enzymatic activity, and the mere shift of the methyl group from position 3 (in creatinine) to position 5 (in 5-methylglycocycamidine) diminished the rate of decomposition very greatly. Acetyl creatinine and glycocycamidine were also slightly decomposed.

The "NC" enzyme preparation was also tested against a number of substances very closely related to creatinine but which do not give the Jaffe reaction with alkaline picrate. In these cases, the activity of the enzyme was tested by the determination of a characteristic product of the reaction. Urea was selected since it was found to be the most constant product of the action of the NC enzyme upon creatinine.

TABLE I

DECOMPOSITION BY NC ENZYME OF JAFFE-REACTIVE SUBSTANCES
RELATED TO OR ASSOCIATED WITH CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND*	PERCENTAGE DECOMPOSITION MEASURED BY CHANGE IN JAFFE REACTION
	<i>per cent</i>
Creatinine	100
5-Methylcreatinine	0
Dimethylcreatinine	0
† Acetylcreatinine	10†
4-(or 5-) Benzoylcreatinine	0
5-Benzylcreatinine	0
2-Benzylcreatinine	0
Glycocylamide	10
5-Methylglycocylamide	10
Hunter's chromogenic substance in human erythrocytes	0

* The nomenclature is that used by Greenwald (1925)

† Acetylcreatinine does not undergo further destruction when the incubation is prolonged. This is different from the action with glycocylamide and 5-methylglycocylamide, since both these compounds may be completely decomposed if the incubation is continued for some hours

TABLE II

PRODUCTION OF UREA BY ACTION OF NC ENZYME UPON
NON-JAFFE-COMPOUNDS RELATED TO CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	PRODUCTION OF UREA*
Creatinine	+
Creatine	+
Methylhydantoin	0
Methylhydantoic acid	0
Hydantoin	0
Guanidineacetic acid	+
Methylguanidine	+
Arginine	+
Sarcosine	0
Guanidine	Trace

* + indicates the production of approximately equivalent amounts of urea

TABLE III

ACTION OF "HR" ENZYME PREPARATION ON COMPOUNDS RELATED TO CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	PERCENTAGE DECOMPOSITION MEASURED BY JAFFE REACTION
	<i>per cent</i>
Creatinine	100
5-Methylcreatinine	0
4- (or 5-) Benzoylcreatinine	0
5-Benzylcreatinine	0
2-Benzylcreatinine	0
Dimethylcreatinine	0
5-Methylglycocyamidine	0
Glycocyamidine	15

The results presented in Table II indicate that creatine, guanidine-acetic acid, methylguanidine, and arginine are decomposed at about the same rate as creatinine. It would appear, therefore, that the ring structure of creatinine is but a small factor in determining the specificity of the enzymatic action. On the contrary, the presence of a guanidine-like unit in the molecule appears to be an important determinant of the specificity, since the replacement of one "NH" group by the CO linkage (as in the change from creatinine and creatine to methylhydantoin and methylhydantoic acid) prevents any reaction with the enzyme. It is also interesting that the absence of the methyl group in guanidine (as compared with methylguanidine) markedly reduces the production of urea, as does the shift of the methyl group in creatinine from the 3 to the 5 position.

Cultures of another soil bacillus "HR" have also yielded an enzyme system which attacks creatinine and which is even more specific than the one previously studied. It is shown in Table III that, of the compounds giving the Jaffe reaction which were tested, glycocyamidine is the only one besides creatinine which is attacked by the enzyme, and the rate of its decomposition is far slower than in the case of creatinine, in consideration of the excess of enzyme employed, the inability of the "HR" enzyme to decompose 5-methylglycocyamidine is especially striking.

To determine the effect of the "HR" preparation upon compounds

TABLE IV

ACTION OF "HR" ENZYME ON NON-JAFFE-REACTIVE COMPOUNDS
RELATED TO CREATININE 0.200 MG OF COMPOUND WAS
USED IN EACH INSTANCE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	UREA + NH ₃ NITROGEN OBTAINED BY HYPO- BROMITE METHOD	PERCENTAGE DECOMPOSITION
	<i>mg</i>	<i>per cent</i>
Creatinine	0.0740	100
Creatine	0.0654	100
Glycocyamidine	0	0
Glycocyamine	0	0
Methylhydantoin	0	0
Methylguanidine	0	0
Guanidine acetate	0	0
Arginine	0	0

related to creatinine, but which do not give the Jaffe reaction, advantage was taken of the fact that, when creatinine is acted upon by the enzyme, all the nitrogen is recovered as ammonia plus urea. It is shown in Table IV that the enzyme does not attack glycocyamine, methylguanidine, or arginine, which are decomposed by the "NC" enzyme. Glycocyamidine does not yield any demonstrable amount of urea or ammonia, it will be remembered, however, that this substance is slowly attacked as determined by disappearance of the Jaffe reaction (Table III). It appears, therefore, that the "HR" preparation slowly opens the ring structure of glycocyamidine, but does not decompose the compound further.

With the help of these bacterial enzymes, it has been possible to develop analytical techniques which are highly specific for creatinine and which have been used by several workers for the study of the metabolism of this substance.⁶

Let us mention in passing that it is possible to extract in solution from the cells of one of the creatinine decomposing cultures an enzyme—an anhydrase—which converts creatine into its anhydride creatinine.⁷ This reaction offers an opportunity for the study *in vitro* of (a) the enzymatic production of a biologically important cyclic compound from an aliphatic one, and (b) the enzymatic combination of an amino and a carboxyl group to form the CO-NH linkage. Preliminary experi-

ments indicate that, like the creatinine oxidase, the creatine anhydrase exhibits a great specificity with reference to the substrates which it affects

The decomposition of the capsular polysaccharides of pneumococcus by bacterial enzymes Virulent pneumococci differ from the avirulent variants of the same bacterial species by the presence of a capsule surrounding the cell. Encapsulated pneumococci can be divided into a number of different serological types, and the type specificity is associated with differences in the chemical composition of the capsular material. The capsular substances of several types of pneumococci have been obtained in a reasonable state of purity and all of them belong to the class of polysaccharides^{8 9 10}

On the basis of immunological evidence, it appears therefore that the capsular polysaccharides of the different types of pneumococcus are of paramount importance in determining the serological specificity and conditioning the virulence of these organisms. It was felt that the evidence for this view would become even more convincing if one could obtain specific reagents, enzymes for instance, which, by decomposing the capsular polysaccharides, would render the encapsulated pneumococci inagglutinable in the homologous antisera, and at the same time alter their virulence.

As far as is known, the capsular polysaccharides of pneumococci are not decomposed by enzymes of animal or plant origin, nor are they attacked by common species of bacteria, actinomycetes or molds. It was possible, however, to isolate from soil a new bacterial species, a sporulating bacillus, which hydrolyzes the specific polysaccharide of Type III pneumococcus. A soluble enzyme, capable of catalyzing the same reaction, was separated from cultures of this soil bacillus grown under well defined experimental conditions^{11 12 13 14}

The enzyme depolymerizes the Type III capsular polysaccharide to the aldobionic acid stage. As a result of enzymatic hydrolysis, the capsular substance loses the ability to react *in vitro* with the specific antiserum obtained by immunizing experimental animals with the Type III capsular antigen.

It can be demonstrated by staining reactions that the addition of active enzyme to a suspension of living encapsulated Type III pneumococci causes the disappearance of the capsule, the specific agglutinability of the bacterial cells in the Type III antiserum is at the same time greatly

TABLE V

SPECIFICITY OF THE PROTECTIVE ACTION OF TYPE III ENZYME

(Reprinted from the *Journal of Experimental Medicine*)

INFECTING DOSE OF PNEUMO- COCCUS	ENZYME (LOT 4-a) J E C C			NO ENZYME		
	Pneumo- coccus Type I	Pneumo- coccus Type II	Pneumo- coccus Type III	Virulence-controls		
				Type I	Type II	Type III
cc						
0 1			S			
0 01			S			
0 001			S			
0 0001	D20	D34	S			
0 00001	D34	D34	S	D22	D36	D34
0 000001	D34	D34	S	D34	D36	D34
0 0000001				D34	D20	D72

S = survived

D = Death of animal, the numeral indicates the number of hours before death

— = not done.

impaired. It is important to mention, however, that the enzyme does not kill the bacterial cells, in fact Type III pneumococci grow readily in media containing the enzyme, but they are deprived of their capsules, when the decapsulated cells are now transferred to a new medium not containing the enzyme, the capsule again reappears and restores to the pneumococci their full virulence and their agglutinability in Type III antiserum. It is clear therefore that the action of the enzyme is directed against the preformed capsular polysaccharide, but does not affect the metabolism of the bacterial cell.

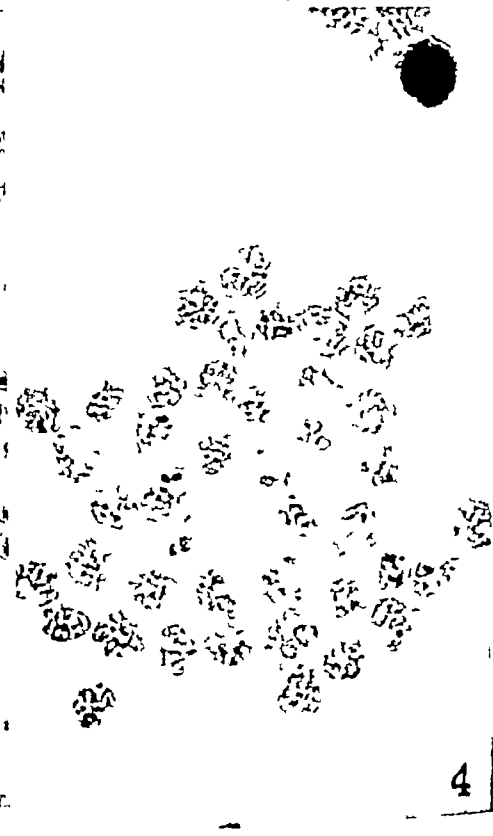
Enzymes capable of attacking the capsular polysaccharides of other pneumococcus types have now been obtained from different strains of soil bacteria^{16, 16, 17, 18, 19}. Several of these enzymes exhibit a remarkable specificity, and can differentiate between polysaccharides which give cross reactions in immune antisera, for instance, the polysaccharide of gum acacia which reacts in Type III pneumococcus antiserum is not affected by the enzyme which hydrolyzes the Type III polysaccharide.¹³ Even more striking is the difference between the enzymes attacking the polysaccharides of Type III and Type VIII pneumococcus. Both these substances are composed of glucose and glucuronic acid in different ratios, and because of this chemical relationship, they exhibit a certain

amount of cross reaction in immune sera^{20 21} On the contrary, the bacterial enzymes developed against each one of the polysaccharides fail to attack the other,¹⁰ in other words, the enzymes are even more specific than are the antibodies obtained by immunization of experimental animals

Not only are the bacterial polysaccharidases capable of hydrolyzing the capsular substances *in vitro*, but they exhibit the same activity *in vivo* In fact, they can protect experimental animals against infection with virulent pneumococci²² In view of the specificity which the enzymes exhibit *in vitro*, it was to be expected that the protection induced would also exhibit a specificity determined by the chemical nature of the capsular polysaccharide of the particular type of pneumococcus used for infection It is shown in Table V, for instance, that the enzyme which decomposes the Type III capsular substance can protect mice against infection with 1,000,000 fatal doses of pneumococci of this type, but is entirely ineffective against pneumococci of other types The same polysaccharidase exhibits also a curative effect on the dermal infection of rabbits,^{23, 24} as well as on the experimental pneumonia in monkeys of the *M cynomologos* species, produced with Type III pneumococci²⁵

The mechanism of the protection so induced is revealed by a microscopic study of the peritoneal exudate of mice during the course of infection with Type III pneumococci²² The progress of events can be seen in photomicrographs which illustrate the differences in cellular reactions of treated and untreated mice, 2 and 4 hours after injection of one million fatal doses of pneumococci Two hours after infection, the peritoneal exudate of the untreated mouse (Fig 1) showed numerous encapsulated cocci free in the fluid In contrast to this, the pneumococci in the enzyme treated animal at this time (Fig 2) were devoid of capsules, and only naked bacteria were visible, many of which were already engulfed by leukocytes At the end of 4 hours, the number of encapsulated pneumococci had increased in the peritoneum of the untreated mouse (Fig 3), in the treated mouse only an occasional decapsulated organism was seen outside the leukocytes whereas many could be seen within the phagocytic cells (Fig 4) It is obvious therefore that the protective action of the enzyme lies in its capacity to decompose the capsular substance of the infectious agent

In summary three different tests have been employed to demonstrate the action of the polysaccharidases (a) decomposition of the purified



capsular polysaccharides, with attendant loss of their specific precipitability in homologous antiserum, (b) destruction of the pneumococcus capsule, both *in vitro* and *in vivo*, (c) protection of experimental animals against infection with virulent pneumococci. All these reactions are type specific. They confirm beyond doubt that the pneumococcus capsules consist of the specific polysaccharides and the latter substances determine the serological specificity of pneumococci and condition their virulence. The polysaccharidases are neither bacteriolytic, nor bactericidal, it is by destroying the protective capsules of the virulent pneumococci that they render the bacteria susceptible to the phagocytic action of the cells of the host, and determine the recovery of the animal.

It is clear that two properties of the enzymes have made possible their application to the study of pneumococcus infections, (a) their specificity, (b) the fact that they can function under physiological conditions. Microbial enzymes have also been used with advantage in studying the chemical nature of bacterial antigens, and there are many other biological problems the analysis of which would be greatly facilitated if enzymes specific for certain substrates were available. The addition of the test substrates to soil or sewage, for instance, will reveal in all cases the existence of microorganisms capable of decomposing them. By isolating these microorganisms in pure culture from the natural

LEGENDS FOR PHOTOMICROGRAPHS

FIG 1 Photomicrograph of a stained preparation of the peritoneal exudate of a mouse 2 hours after the intraperitoneal injection of 0.01 cc. of a virulent culture of Type III pneumococcus. The bacteria show well-defined capsules and no evidence of phagocytosis is seen. Many polymorphonuclear and a moderate number of mononuclear leukocytes are present. Gram stain $\times 1000$.

FIG 2 Photomicrograph of a corresponding preparation of the exudate of a mouse 2 hours after receiving the same amount of culture together with 0.5 cc. of a preparation of the specific enzyme. The bacteria are devoid of capsules. Polymorphonuclear leukocytes predominate and phagocytosis is evident. Gram stain $\times 1000$.

FIG 3 Photomicrograph of a stained film of the peritoneal exudate of a mouse 4 hours after injection with 0.01 cc. of culture alone. The bacteria are increased in number, encapsulated, and extracellular. The cellular elements are polymorphonuclear and mononuclear leukocytes in about equal numbers. Gram stain $\times 1000$.

FIG 4 Photomicrograph of a corresponding preparation of the exudate of a mouse 4 hours after receiving the same amount of culture together with 0.5 cc. of a preparation of the specific enzyme. Marked phagocytosis has occurred and only an occasional organism is seen outside the accumulated leukocytes, nearly all of which are of the polymorphonuclear type. Gram stain $\times 1000$.

[Differences in the density of the backgrounds of these four figures are due to the use of color screens in the photographic reproductions. This technique however, alters none of the essential details observed in the original microscopic preparations. (Reproduced by the courtesy of the *Journal of Experimental Medicine*)]

sources, and growing them under appropriate conditions, it should often be possible to prepare enzymes adapted for use as specific physiological reagents

A selective bactericidal principle extracted from cultures of a sporulating bacillus The preceding discussion has considered the isolation from natural sources of microorganisms capable of decomposing well-defined organic compounds (creatinine, polysaccharides, etc.) It appeared possible that there also exist microorganisms capable of attacking not only soluble, isolated substances, but also the intact living cells of other unrelated microbial species. Specifically, an attempt was made to recover from soil, microorganisms that could attack the living cells of the pathogenic Gram-positive cocci.²⁶ To achieve this end, suspensions of living pneumococci, streptococci, and staphylococci were added to a soil mixture which was maintained at neutral reaction under aerobic conditions, in the hope that there would develop in the soil preparation a microbial flora antagonistic to the Gram-positive cocci. In fact, it was possible to isolate from the soil preparation an aerobic sporulating bacillus which can multiply at the expense of the living cells of Gram-positive bacteria. Cultures of this soil bacillus have yielded a soluble principle which kills the susceptible bacterial species,²⁷ the following discussion deals with the nature, properties and activity of this bactericidal principle

The bactericidal principle of the soil bacillus can be obtained in a protein-free form which is soluble in alcohol and acetone, but insoluble in water and ether.²⁸ From the alcohol soluble fraction there have been obtained as crystalline compounds three well-defined chemical entities all of which exhibit bactericidal action *in vitro*, they have been called graminic acid, gramidinic acid, and gramicidin with respective molecular weights of 900, 1000, and 1400.²⁹⁻³⁰ Although the complete structure of these substances is as yet unknown, it can be stated at this time that all of them consist largely of amino acids probably combined as polypeptides. Gramicidin which has been most carefully studied contains 2-3 tryptophane residues per molecule, a large percentage of the other amino acids appear to be present in the *d* (so-called unnatural) form, gramicidin also contains an aliphatic fatty acid but contains neither free acid nor basic group. As stated above, the three crystalline substances exhibit a marked bactericidal effect *in vitro*. For instance, 0.005 mg of gramicidin is sufficient to kill 10^9 pneumococci or virulent streptococci

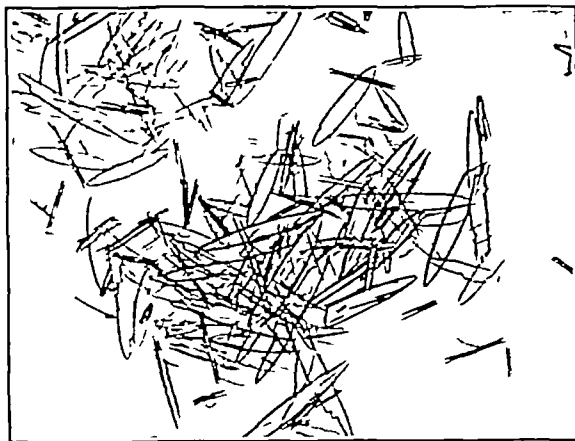


FIG 5 Photomicrograph of crystals of gramicidin
× 225 (Reproduced by courtesy of Dr R D Hotchkiss)

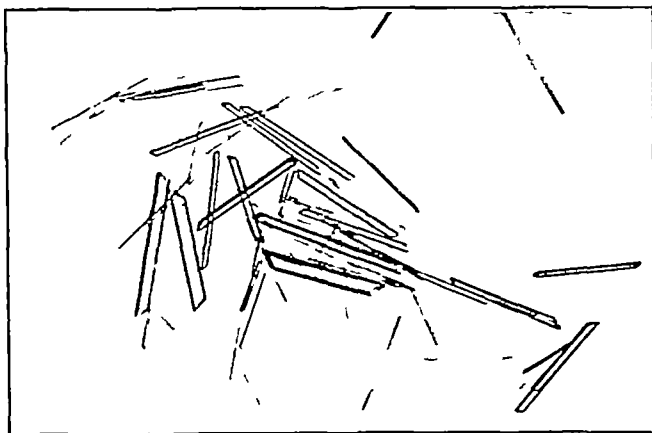


FIG 6 Photomicrograph of crystals of gramicin acid
× 320 (Reproduced by courtesy of Dr R D Hotchkiss)

within 2 hours at 37° C Staphylococci, diphtheria bacilli, aerobic sporulating bacilli, in fact all Gram-positive organisms so far tested, are also readily killed under the same conditions although the amount of bacterial substance required varies from one bacterial strain to the other. On the contrary, none of the Gram-negative bacilli have been found to be susceptible, even to much larger amounts of the substance. Meningococci and gonococci are much more susceptible than the Gram-negative bacilli but more resistant than pneumococci or streptococci, this fact may be of some interest, since bacteriologists have often considered the

TABLE VI

PROTECTIVE ACTION OF CRYSTALLINE FRACTION OF
BACTERICIDAL AGENT

(All mice infected with 10,000 fatal doses of Type I pneumococcus)

MATERIAL	AMOUNT	NUMBER OF MICE	RESULT		
	mg				
Graminic acid	0.016	3	D40	D44	D68
"	0.008	3	D40	D40	D48
"	0.004	3	D40	D40	D40
"	0.002	3	D40	D96	D96
"	0	3	D24	D40	D40
Gramicidin	0.010	3	S	S	S
"	0.005	3	S	S	S
"	0.002	3	D61	D114	S
"	0.001	3	D45	D46	S
"	0	3	D27	D27	D32

S = Survival

D = Death, the numeral indicates number of hours after infection

Gram-negative cocci as intermediary between the Gram-negative bacilli and the Gram-positive organisms

In spite of the great activity which they exhibit *in vitro*, both graminic acid and gramicidin appear ineffective *in vivo*. On the contrary, one single dose of 0.001 to 0.002 mg of gramicidin injected into the abdominal cavity, is sufficient to protect mice against 10,000 fatal doses of pneumococci or streptococci (Table VI). Larger amounts of the material, injected on 3 consecutive days will also protect mice against larger infective doses, or cure them of a well-established infection. The bactericidal substance has proven equally effective against infection with the 5 different types of pneumococci and the 14 different types of hemolytic streptococci (groups A and C) which have been tested, it is permissible to hope, therefore, that it will also prove effective against all virulent strains of these bacterial species irrespective of type specificity, in fact preliminary experiments have recently demonstrated that it does also protect mice against certain strains of staphylococci. On the contrary as could be expected from the *in vitro* experiments, no protection could be obtained against infection of mice with *Klebsiella pneumoniae* (Type B), a Gram-negative bacillus.

Gramicidin is very insoluble in aqueous media, this insolubility may account for the fact that the substance is ineffective against pneumococcus peritonitis in mice when administered by any route (intravenous, intramuscular, subcutaneous) other than the intra-abdominal. Very recently, it has been possible to obtain from autolyzed cultures of the sporulating soil bacillus, a form of the bactericidal substance which is readily soluble in water at neutral reaction, not only does the new preparation cure mice of pneumococcus and streptococcus peritonitis when administered intra-abdominally, but it is also effective by the subcutaneous and intravenous route. Although much remains to be learned about this soluble fraction, it is evident that in some respects it is more effective *in vivo* than the crystalline substance which has been described under the name of gramicidin.

The findings just reported have revealed the existence and to some extent the chemical nature of a new type of bactericidal agent, which, although extremely active against many different species of Gram-positive microorganisms, fails to attack the Gram-negative bacilli. It can be said, therefore, that this new bactericidal principle exhibits a specificity of a peculiar order, one which is correlated with the staining characteristics of the bacterial cells. Since the staining properties are necessarily conditioned by chemical and physical characters of cellular structure, it is perhaps permissible to state that the specificity of the bactericidal agent is related to some structural difference between the Gram-positive and the Gram-negative cells. An analysis of the mechanism of the bactericidal action³¹ may therefore reveal important facts concerning cellular structure, this knowledge in turn may indicate what type of chemical structure can be expected to exhibit affinity for the cellular structure of the different bacterial species and may suggest new avenues of approach to the problem of antiseptics. It is also of obvious importance to establish the chemical differences between gramicin acid and gramicidin which determine that only the latter is active *in vivo*, whereas both are equally active *in vitro*. This knowledge will give us a clue as to the factors which allow an antiseptic to remain active in the presence of animal tissues, and which thus render it a therapeutic agent.

Finally it is permissible to hope that one will also discover in nature microorganisms antagonistic to other types of pathogens and that the active substances by means of which they exert their antagonistic effect will be isolated. These agents may not themselves be effective in the

animal body. An understanding of their chemical structure and of the mechanism of their action should, however, give the bacteriologist and the chemist useful information and new compounds for the development of chemotherapy on a rational basis.

The adaptive production of enzymes by bacteria. It is apparent that the biologist will discover in the microbial world a great variety of useful reagents. On the other hand it is also true that microbial life has revealed a number of physiological processes of general biological significance. For instance, cultural conditions greatly affect the enzymatic constitution of the microbial cell. In some cases in particular, the production of a given enzyme is stimulated when the substrate which it attacks is a component of the culture medium. The bacillus which hydrolyzes the capsular polysaccharide of Type III pneumococcus does not form the specific enzyme when cultivated in ordinary peptone media (in which growth is very abundant), whereas the polysaccharidase is readily produced when the same organism is compelled to use the specific polysaccharide in the course of its growth^{11, 12, 13}. Similarly, the "NC" culture which attacks creatinine grows abundantly in peptone solutions, but forms the creatinine oxidase only when creatine or creatinine is a constituent of the culture medium.^{5, 7} Karstrom designated as "adaptive" those enzymes which are produced as a specific response to the presence of the homologous substrate in the culture medium, he differentiated them from the "constitutive" enzymes which are always formed by the cells of a given species, irrespective of the cultural conditions.³³

Adaptive enzymes exhibit a great specificity with reference to the substrates which they attack, a property which suggests their use in the analysis of biological problems, it is of practical importance therefore, to develop satisfactory techniques for their production. One may wonder also whether the readiness with which microorganisms selectively change their enzymatic constitution in response to changes in the environment may not be of importance in determining the pathology of infectious diseases. Is it not possible that a pathogenic agent growing in living animal tissues may differ in important respects from the same agent grown in laboratory media? In other words, the pathogenic agent may produce during the infectious process, a number of substances which do not appear during growth in the standard laboratory media, and which are the result of the reaction between the para-

site and the tissues of the infected host. These products might account for some of the obscure reactions of infection.

In any case, the very mechanism of production of adaptive enzyme by microorganisms challenges the bacterial physiologist, nothing is known of this mechanism.^{32 33 34 35} It seems established that the change in enzymatic construction which results in "adaptation" does not necessarily require the production of new cells. Although production of adaptive enzymes has been described to occur in the absence of cellular division, all evidence available indicates that this formation always involves the synthesis of new protoplasm. It is possible that the synthetic process is, so to speak, oriented or guided by the chemical structure of the substrate, which thus determines the specificity of the enzyme evoked. And it is a common fact, as already pointed out, that adaptive enzymes exhibit a remarkable specificity toward the substrates which stimulate their production.

The phenomenon of adaptive production of enzymes offers great practical possibilities to the bacteriologist. Even more important perhaps, it brings him back into the main channels of biological thought, to the biological problem "par excellence," the problem of adaptation. The study of the mechanism whereby microorganisms produce those enzymes which appear as an adaptive response to the presence of the homologous substrates in the culture medium, bids fair to throw light on some of the reactions involved in specific adaptation.

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THE PRESENT STATUS OF THE TREATMENT
OF SUBACUTE BACTERIAL ENDOCARDITIS*

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I am presenting an analysis of methods of treatment of subacute bacterial endocarditis, it is well at the outset to say a few words about the criteria for diagnosis. Only reports of those patients having positive blood cultures of *Streptococcus viridans* will be included in this discussion. It is, of course, generally known that in many patients it is not possible to recover the organisms from the blood, yet at autopsy the characteristic pathological changes are found on the heart valves and organisms can be recovered from the valves. For the purposes of analysis, however, such cases will have to be excluded from our discussion. Organisms other than strains of *Streptococcus viridans*, namely staphylococci, *Streptococcus hemolyticus* and gonococci, have been described as causing subacute bacterial endocarditis. One could easily see how difficult it would be if the field were broadened to include these organisms.

It will also be necessary to include only those cases having well-established clinical evidence of endocarditis because, as Hamman¹ pointed out in 1937, it is possible for the streptococcus "to invade the blood stream when there is infection in the upper respiratory tract and no doubt less frequently with infections located elsewhere. Therefore, the presence of bacteria in the blood during the course of a febrile reaction does not signify that the endocardium has become infected, unless at the same time there is undisputed evidence of a valvular lesion or a congenital defect and other characteristic symptoms of bacterial endocarditis are present." Another important bit of confusion which enters into the discussion of treatment is the difficulty many times in differentiating between a recurrence of rheumatic activity and subacute bacterial endocarditis. This difficulty extends even to the blood culture. In 1929 Cecil, Nicholls and Stainsby² recovered *Streptococcus viridans*

* Read November 26, 1940 at The New York Academy of Medicine before the New York Heart Association.

strains from the blood of rheumatic patients in a high percentage of cases. In 1933 Callow³ reported an incidence of 70 per cent positive blood cultures in rheumatic active patients, and of these 35 per cent showed *Streptococcus viridans*. It should be stated, however, that Cecil, Nicholls and Stainsby and Callow did not obtain the organisms from the blood stream of patients with rheumatic fever with as great ease as is usually possible in a fresh case of subacute bacterial endocarditis. It is evident, then, that some cases of supposed subacute bacterial endocarditis superimposed on old rheumatic valves are in fact cases of recurrent rheumatic activity and any treatment which has apparently caused the infection to subside merely coincided with the natural and spontaneous remission of the rheumatic infection. This is especially true if organisms are recovered with difficulty from the blood stream or if special techniques are used. It is obvious, also, that the disease must be well along its course because early diagnosis is difficult and often impossible. Treatment, therefore, given to the so-called early cases, although desirable, cannot be decisive because the diagnosis is frequently open to question.

Subacute bacterial endocarditis is a disease in which spontaneous remissions are said to occur. It has not been my privilege, however, to have ever witnessed such a case. Every patient with this disease that I have seen on the Third Medical Division at Bellevue Hospital and in my private practice since 1921 has finally succumbed. Hamman¹ as late as 1937, said this of Johns Hopkins Hospital: "As far as I know the uniform mortality of the disease at that hospital has not changed during the last 12 years. Certain I am, that no well-established instance of subacute bacterial endocarditis, which has been under my observation has ever recovered." If we exclude the so-called epidemic reported by Oille, Graham and Detweiler,⁴ the largest number of spontaneous remissions is reported by Libman^{5,6}. From his vast experience with this disease Libman gives the incidence of spontaneous recovery as about 3 per cent. He is certain of at least twenty-five cases, and there are probably others among those where a proper follow-up could not be carried on. Capps⁷ is of the opinion that virulence varies from year to year and that since 1924 we have had a much more virulent form of the disease than prior to that date. This is not concurred in by Libman. Granting, then, that spontaneous remissions are possible, this fact must of necessity be considered in the evaluation of any form of treatment.

Many patients reported as benefiting by some forms of treatment,

have eventually died and at autopsy evidence of healing in diseased valves is noted. This is sometimes considered as indicating some beneficial effect of the treatment. However, in the natural course of the disease we find that the attachment of the vegetation is the seat of an organizing reaction like that of healing. In order to be certain that the treatment affected the course of the disease bacteria must be found in the valves themselves. This, taken in conjunction with the healing reaction is evidence of the effectiveness of the treatment. Very few observers have followed this rigid method of control.

Because of the anatomical peculiarities of the characteristic valvular lesion the difficulties in treatment are considerably increased. As Friedman⁸ has pointed out, "The entire process is surrounded by dense fibrin and platelets, deposited by the blood stream, which isolates the proliferating bacteria from the possibility of contact with any agent not dissolved in the blood plasma. Because of these facts, it would be best to consider subacute bacterial endocarditis as an infection characterized by masses of bacteria growing in fibrin, suspended in and yet isolated from the blood stream."

As summarized by Andrews three main difficulties, then, exist in the evaluation of forms of treatment:

- 1 "The difficulty that exists in certain cases in establishing the diagnosis"
- 2 "The possibility of spontaneous recovery"
- 3 "The anatomical peculiarities of the site of the infection and of the lesion, which render the organisms difficult to reach by therapeutic agents"

TREATMENT OTHER THAN WITH SULFONAMIDE DERIVATIVES

Probably no disease has had as many remedies. This fact alone speaks for the futility of most of them. Non-specific supportive treatment will always be of value. These measures include blood transfusions for anemia, supplemental vitamins and minerals in the diet or otherwise, and drugs or physical measures for treatment of symptoms as they arise. In any treatment directed toward the etiological agent this part of the therapy will always be important.

In 1936 Riesman, Kolmer and Polowe⁹ advocated removal of the spleen as a therapeutic procedure. Because in this disease the spleen is often the site of multiple infarctions, they reasoned that the spleen was

a sort of "branch factory," acting as a secondary focus in the multiplication of bacteria. In their opinion, therefore, its removal would make it easier for the normal processes of recovery to take place. Their results are not particularly encouraging, of the four patients operated on, three died, and in the fourth who survived, "No definite diagnosis was arrived at—mural subacute bacterial endocarditis seemed reasonable."⁹ In 1939 Polowe¹⁰ reported one case of apparent cure. In reviewing the protocol of this case I am not convinced that, if our criteria are kept with proper rigidity, this case can be classified as true subacute bacterial endocarditis. It is probable that, with chemotherapy offering the hope it does, splenectomy will fall into the discard.

Even before the days of sulfonamide derivatives many chemical substances have been used as specific agents, arsenic compounds in particular. Capps⁷ reported four cures with sodium cacodylate. He expresses considerable surprise and also admits that after these four cases he has never been able to get the same satisfactory results. Arsenical compounds are known to exert a powerful stimulus on the reticulo-endothelial system, resulting in increased phagocytosis and in the production of immune substances. In this connection the experience of Lippman¹¹ is interesting. He gave a patient with subacute bacterial endocarditis sulfanilamide, neoprontosil and sulfapyridine with only slight improvement. On giving ammonium hepten-chlorarsonate, the temperature became normal, there were no further emboli, and the patient had been up and about for three and one-half months at the last observation. In contrast to this is the fact that seven patients in a series of 250 patients soon to be reported by Kelson¹² were given arsenicals with no apparent benefit.

THE SULFONAMIDE DERIVATIVES

Naturally the first drug to be used of the series was sulfanilamide. Long¹³ has five recoveries out of 120 patients treated. "All of these patients are in as good health as their underlying cardiac condition will permit them to be, and they have gone on an average of two and a half years without any recurrence of their infection." Heyman¹⁴ reports a remission of 18 months in a patient whose underlying heart disease is patent ductus arteriosus. In general, however, results with this drug are not encouraging. Solway and Pritzker¹⁵ report a death in spite of intensive treatment. Spink and Crago¹⁶ report twelve cases with two apparent recoveries. However, one of these patients was infected with *Staphylococ-*

cus aureus, so we can actually count one cure in their series. They conclude that the treatment is of doubtful value. Major¹⁷ used other members of the sulfonamide group as well as sulfanilamide and reports two apparent cures after the disease had been quiescent one year, and nine months respectively. The first patient received neoprontosil and prontosil and then sulfapyridine. The second patient received sulfapyridine alone. One other patient with advanced heart disease died of congestive heart failure and autopsy showed healed mitral and aortic valves. This patient had received prontosil and sulfanilamide. The eventually fatal termination in three other patients was in no way influenced by sulfapyridine and prontosil. Andrews¹⁸ reports a recovery following intensive therapy with sulfapyridine. However, his patient had one negative blood culture. No others were taken. In April 1940 Kinell and Ernstene¹⁹ from the Cleveland Clinic reported five patients with subacute bacterial endocarditis treated unsuccessfully with sulfapyridine. Two of these cases were identified with *Streptococcus viridans*, two with non-hemolytic streptococci, and the other with an anaerobic streptococcus. Kelson and White's²⁰ experience with the sulfonamide derivatives alone was disappointing. In forty-six patients receiving sulfanilamide an occasional reduction of fever and sterilization of the blood stream resulted, but there was no lasting benefit in any instance. They gave sulfapyridine alone to ninety-seven patients and found that in the majority the temperature was lowered, with frequent sterilization of the blood stream. Except in a single instance, however, these effects were temporary, "escape" occurred in from a few days to two months. The one patient apparently cured was not infected with *Streptococcus viridans* but with the gonococcus, together with a non-hemolytic anaerobic streptococcus. In nineteen cases, sulfathiazole was given and only temporary improvement was noted in four cases.

It might be well at this point to consider briefly the chemotherapeutic problem presented by this disease. In 1938 Friedman⁵ made a study of the fibrin factor in its relation to subacute bacterial endocarditis. At the same time he described the properties any chemotherapeutic agent must have to be effective in this disease. They are well worth quoting here:

- 1 "It or its *in vivo* breakdown products must not be neutralized by the proteins of the blood stream to such an extent that the bactericidal properties are nullified.

- 2 "It must be able to permeate the fibrin mass which surrounds the organism
- 3 "It must be able to remain in the blood stream long enough and in sufficiently high concentration so that it can permeate the fibrin in a quantity sufficient for bactericidal purposes and at the same time not affect the host adversely "

The sulfonamide derivatives generally used satisfy the first criterion but fail in the other two. The inability of sulfanilamide, sulfapyridine and sulfathiazole to penetrate blood clots *in vitro*, as shown by Duncan and Faulkner,²¹ is in accord with the clinical observation of their inability or difficulty in penetrating the fibrin network on the valves in subacute bacterial endocarditis. These observers, however, believe that even with this handicap, eradication of the infection is possible because "In the course of time all of the preexisting thrombi should become organized into fibrous scar tissue while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus, conditions will tend to become less and less favorable for growth of the organism if an effective drug is taken continuously over a long period of time." Whether or not this theory is correct could not be tested from the published case reports. Insufficient data on methods of dosage and amounts as well as an inadequate number of observations on blood level of the drug, if these observations were made at all, made it impossible to analyze the results of treatment.

An ingenious method of getting around this problem of the fibrin clot is the technique developed and reported simultaneously by Kelson and White,²⁰ and by Friedman, Hamburger and Katz.²² The latter authors report one case with an unfavorable result, whereas Kelson and White report favorable results in two of six patients with subacute bacterial endocarditis. The method now used by Kelson and White is as follows:

Sulfapyridine is given in large doses to bring the blood level above 5 mgm per 100 cc for 4 to 7 days. Heparin is then given by uninterrupted intravenous drip day and night for 14 days. The solution of heparin was originally made as follows: the contents of a 10 cc vial of heparin (10,000 units) was added to 500 cc of physiological saline. However, because of the high salt intake with this method, edema developed, therefore, the present technique is to use distilled water with 5 per cent of glucose and heparin. Occasionally, in patients already

edematous, 10 per cent glucose, which is mildly dehydrating, is used instead. Kelson and White now have a total of twenty-seven patients treated with this method. Three patients are well and physically active several months after completing therapy, one patient was well and active for a time but had a recrudescence of his disease following a tooth extraction, and another patient died in congestive heart failure. At autopsy this patient showed complete healing of the bacterial lesion with complete absence of bacteria in the lesion.

The use of heparin is based on the *in vitro* experiments that heparin will arrest the deposition of platelets and fibrin. Granting that this also takes place *in vivo* on the heart valves, such action prevents organisms from becoming enmeshed in fibrin to such an extent that they cannot be reached by the sulfonamide derivatives.

Kelson and White²⁰ do not believe that this method causes a tendency to spontaneous hemorrhage, particularly cerebral hemorrhage. Although they had two cerebral deaths in their twenty-seven patients, they are of the opinion that the incidence of hemorrhage is no greater than occurs spontaneously in the natural course of the disease. In explaining the high percentage of unsatisfactory results they point out that the previous use of sulfonamide derivatives, particularly sulfapyridine, may render the organisms fast to the drug and thus prevent complete sterilization of the blood stream and heart valves. As far as I know, Kelson and White are the only authors reporting favorable results with this method. Friedman, Hamburger and Katz²² and more recently Kleiber²³ report fatalities. Long¹³ states that he has not been impressed by heparin and considers it a dangerous adjunct to treatment.

Another method of approach is the combination of intensive treatment with a sulfonamide derivative plus the raising of the body temperature either by typhoid-paratyphoid vaccine as advocated by Solomon,²⁴ or the use of hyperthermia by physical means as described by Bierman and Baehr.²⁵ The experimental basis for this work was furnished by H. J. White and Parker.²⁶ They demonstrated that the effectiveness of sulfonamide derivatives increased considerably with a rise in temperature. Solomon's technique is to give sulfapyridine in large doses until a high blood level for the drug is reached, and then to give typhoid-paratyphoid injections intravenously nightly for seven nights. Solomon was kind enough to give me his final figures, of seventeen patients who received treatment, five have apparently recovered

In reviewing the protocols, however, we find only three of these had *Streptococcus viridans* in the blood stream, one other case had non-hemolytic streptococcus and in the other there was merely the statement that the blood culture was positive. All five recoveries took place in the first eight cases studied, there were no recoveries in the last nine cases. It may be said in all fairness, however, that only four of these nine were considered by Solomon to have been adequately treated. Bierman and Baehr²⁵ report the use of the combination of chemotherapy, either sulfanilamide or sulfapyridine with physically induced elevation of the body temperature. Out of sixteen patients, each of whom received six or more bouts of temperature elevation in conjunction with medication, but two made recoveries, and only one of these was due to *Streptococcus viridans*, in the other patient *B. influenzae* was isolated from the blood stream. In still another case a patient has made an apparent recovery for 2 months, but the authors consider this as too short a time to make a positive statement as to recovery. There is some danger connected with the technique, namely a rapid heart rate, hyperexia, rapid respiration. In contrast to the reports of Solomon²⁴ and of Bierman and Baehr²⁵ we have the report by Krusen and Bennett²⁷ of six patients unsuccessfully treated with sulfanilamide and hyperthermia.

Such is the present status of the treatment of subacute bacterial endocarditis. No form of therapy which at present seems to offer some hope of cure in a small proportion of the cases has received the really crucial test of new therapeutic procedures, namely confirmation of the results by other investigators. At best all we expect at the very outside from these newer forms of treatment is that an occasional patient may survive, whereas, before, there was an almost uniformly fatal ending. One must consider, also, the occurrence of spontaneous remissions and even cures at certain times in the evaluation of any form of treatment. It is indeed curious that all observers reporting cases seem to have the greatest number of recoveries in the first few cases. Solomon had five recoveries in the first eight cases, none in the next nine. Long had five recoveries in the first fifty cases and none in the next seventy. Kelson and White had two recoveries in the first six cases and only one more recovery in the next twenty-one cases. Is this merely a peculiar coincidence, or might it be related to the fact that subacute bacterial endocarditis may be due to a number of different strains of *Streptococcus viridans*, strains whose virulence varies greatly? May not certain strains

respond easily to specific forms of therapy or even permit spontaneous recovery? Most observers have neglected to identify the particular strain of *Streptococcus viridans* in each case, so that for the present these questions must remain unanswered. However, there is experimental evidence to show that the identification of the particular strain is important in regard to virulence.

Fox⁶ studied the relationship of strains of green streptococci to the clinical character of subacute bacterial endocarditis and on the basis of his work was able to make the following classification:

Group 1 was characterized clinically by a rapid, stormy course with death in a few months. The strains isolated were salivarius and equinus corresponding to Lancefield's human group.

Group 2 was characterized clinically by a slow course ending with an episode that led to death. The strain isolated was a human form of a rough and G type of *Streptococcus non-hemolyticus*.

Group 3 was characterized by a slowly progressive course with marked anemia and cachexia so that the patient died without any flagrant episodes. Two types of organisms were found: *Streptococcus ignavus*, the human smooth form, and *Streptococcus non-hemolyticus* number 1, a rough non-human form.

Group 4 is the most interesting group because here we have the recurrent cases and possibly those that may be cured. Most of the cases in this group were due to *Streptococcus fecalis* and one to *Streptococcus salivarius*.

In general one may say that the slower the course the more apt is the organism to be of the non-human type.

In May of this year Swain⁷ described the results of treatment of four patients with sulfonamide compounds and correlated the results with the strains of streptococci. In simple *in vitro* tests he found that the two strains isolated from cases clinically influenced by treatment were susceptible to the drug, whereas the strains isolated from the two cases which resisted treatment were also resistant to the drugs *in vitro*. He suggests that the existence of resistant strains of *Streptococcus viridans* may be responsible for the failure of some cases to respond to sulfonamide therapy. It would seem highly important, then, in a therapeutic study to make certain of the strain of *Streptococcus viridans* one is dealing with, and also to study *in vitro* the effect of drugs on the particular organism isolated to determine possible drug resistance of that

TREATMENT OF INFECTIONS BY METHODS OTHER THAN CHEMOTHERAPY*

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THIS review confines itself almost entirely to the use of specific therapeutic serums, referring only when necessary to the synergistic action of antiserums and some of the newer chemotherapeutic agents, and to therapy with bacteriophage. The therapeutic efficacy of bacteriophage and the present status of serums in such diseases as scarlet fever, measles, chicken pox, diphtheria, tetanus, staphylococcal and gas bacillus infections, anthrax and botulism will be discussed. The prophylaxis of tetanus is included because the greater number of investigators have concentrated on the production of active immunity against this infection rather than passive immunity or treatment.

In a general review of this nature, it may be well to state at first some rules which are generally applicable to the therapeutic use of serums in all infections. Most of these are well known, nevertheless, some are not followed, and the importance of others is overlooked.

Therapeutic results are so much better when a sufficient dosage of serum is administered early in the disease that delay must be avoided. It is also important that a large enough dose should be injected initially, as in many instances, if this is done, optimum results will be obtained, and no further injections will be necessary. In some infections, however, the nature of the disease is such that repeated injections of serum are required.

In patients who are critically ill with severe infections, there is no question but that the intravenous route is the method of choice, and might be the only way in which some lives may be saved. The advantage of this is that the therapeutic serum is delivered immediately throughout the entire body, and valuable time is not lost as is the case with serum administered by other routes, when there is considerable delay before absorption into the blood stream occurs.

* Read October 22, 1940 in The Graduate Fortnight of The New York Academy of Medicine

It is not generally realized that it takes from 16 to 18 hours after serum has been injected intramuscularly for the maximum titer of its antibodies to occur in the blood stream, whereas this occurs immediately with intravenous injection. When identical doses are injected by both routes, the titer eventually reached is only half as high after intramuscular as after intravenous injection.

Undoubtedly, intravenous injections are not used more often because there is a definite element of risk of anaphylactic shock or death when even the most carefully prepared animal serum is given intravenously. If the intravenous route is contraindicated because of known sensitivity of a patient, intraperitoneal injection may be used with excellent absorption of antibodies in from 1 to 2 hours, which, with severely ill patients, is the second method of choice.

It seems curious after publication of Platou's¹ excellent work in 1923, and the more recent publication of Banks² that the intraperitoneal injection of serum has not been more generally used. The risk of reactions and shock is not greater than from intramuscular injection. It seems to be the general belief that there is considerable risk from intraperitoneal injection of perforating the bowel and causing peritonitis. This risk is apparently negligible when the injection is properly carried out, and is certainly less than that of delayed serum absorption in desperately ill patients.

There seems to be the general belief, also, that serum injected intramuscularly is retained in the body longer than when the serum is injected intravenously. This is a misconception. Once the peak of absorption has been reached, the serum disappears with the same rapidity as after the same level resulting from intravenous administration. However, it is true that if it is necessary to maintain a high level of antibodies in the circulating blood, and if repeated intravenous injections of serum are contraindicated, the level can be maintained with greater safety by multiple intramuscular injections.

The slowness of absorption of serum after subcutaneous injection makes this a poor method of administration even for prophylaxis.

It is obvious that an ideal therapeutic serum would be one of excellent therapeutic potency, concentrated in small volumes which could be injected intravenously without any risk of untoward reactions even when the injections must be repeated. Unfortunately this ideal has not yet been reached with animal serums even though modern methods of

refining serums have resulted in products much less dangerous than previously employed. The number of instances of shock have been greatly reduced, as well as attacks of serum sickness.

Before injecting an animal serum intravenously, it is imperative to test the individual for hypersensitivity. A drop of normal serum from the same animal species should be injected intracutaneously or instilled into the conjunctival sac. In hypersensitive persons a wheal will form at the site of the cutaneous injection or marked inflammation of the conjunctiva will develop. The eye test is the more sensitive of the two. If hypersensitivity is present, at first a very small dose of the therapeutic serum, beginning with a hundredth or tenth of a cubic centimeter, should be injected subcutaneously. Gradually increasing doses can be given every twenty or thirty minutes, and if no reactions occur the intramuscular route can be used until the full therapeutic dose has been administered.

There are several therapeutically efficient human serums to be discussed later, which, when properly prepared, can be administered intravenously in large amounts, as extensive experience has shown, without fear of causing severe reactions, and with only the occasional occurrence of a mild or moderate reaction.

In addition to the specific treatment, all the accepted methods of general treatment should be carefully carried out, including quiet and protection of the patient, the provision of sufficient rest and sleep, good nursing care, special attention to proper nourishment, the prevention of dehydration, acidosis or alkalosis and avoidance of hypostasis.

SCARLET FEVER

There are two serums available for the treatment of scarlet fever, convalescent scarlet fever serum (human) and scarlet fever antitoxin (animal). In recent years my interest has been concentrated on the study of the effectiveness of human convalescent serums, including that of scarlet fever.

Convalescent scarlet fever serum is prepared from blood obtained from individuals recently recovered from scarlet fever and up to a period of four months after the onset of the disease. The serum from thirty or more individuals is pooled so as to produce a polyvalent serum. Only Wassermann-negative serum is used, and care is taken to prevent even a faint trace of hemolysis. The regulations of the U. S. Public Health

Service are carefully followed, including sterility tests, and safety tests on animals

Convalescent scarlet fever serum is therapeutically efficient and when administered early in the disease in sufficient quantities will cause subsidence of the disease in from 12 to 24 hours in 75 to 85 per cent of the individuals treated, and somewhat slower, less complete results in most of the remainder ^{3, 4, 5, 6, 7} These results refer to the intravenous injection of serum within the first 36 hours after the onset, and are frequently truly dramatic, with the conversion of a desperately sick, toxic child into a convalescent one. Toxicity disappears, temperature drops an average of three degrees Fahrenheit, and not infrequently reaches normal. Vomiting and diarrhea, when present, disappear, the rash begins to fade and the usual complications are reduced to one-third in number and are less severe in intensity when they do appear.

This human serum has the advantage that it can and should be administered intravenously with practically no risk of causing untoward reactions. In an extensive experience in different parts of this country not a single instance of anaphylactic shock occurred. Sensitization to subsequent injections of human serum apparently has not been produced, and mild, delayed serum sickness occurs in not more than one-half to one per cent of the patients.

Usually only one intravenous injection is required to obtain these results when the serum is administered early in the disease and before complications have developed. If, however, complications are already present, or if the patient is brought to the hospital in the later stages of the disease, several injections may be needed at one or two day intervals.

The intravenous dosage is 20 cc. in children up to the age of five, 40 cc. in those from five to ten years, 60 cc. in those from ten to fifteen years, and 80 to 100 cc. in large adolescents or adults. Similar but less rapidly occurring improvement can be obtained from intramuscular injections, but the dosage should be definitely larger.

Although the pooled serum contains both isoagglutinins, there need be no fear from the intravenous injection of incompatible agglutinins, as has been demonstrated thousands of times. Whereas the danger of injecting incompatible cells is well known, this does not apply to the injection of agglutinins. This was also brought out recently at the meeting of the American Human Serum Association including some studies

in our laboratory, which demonstrated that even after the injection of large quantities of incompatible serum, the incompatible agglutinins disappeared from the circulation immediately

It has been demonstrated in some studies with Elizabeth Moore⁸ that convalescent scarlet fever serum contains an appreciable amount of bactericidal substances against Group A hemolytic streptococcus, as well as antitoxin to erythrogenic toxin. Opsonins and antistreptolysin are also present

The amount of antitoxin present in convalescent scarlet fever serum is small (averaging about 10 units per cc) as compared with the antitoxic content of scarlet fever antitoxin (animal). Therefore, the amount of antitoxin in the doses of convalescent serum which have been described is much less than when animal antitoxin is used. Since the therapeutic response to convalescent scarlet fever is as good as or better than that to large doses of animal antitoxin in the experience of Top⁹ and others,^{3, 4, 5, 6, 7} this efficiency must be due to bactericidal and other antibodies which are present in convalescent serum and not present in animal antitoxin, as shown also by Platou and Dwan¹⁰

Animal scarlet fever antitoxin will also produce excellent therapeutic results, and several commercial serums are available which are superior to those previously produced, in that severe reactions and delayed serum sickness occur in a smaller number of individuals. There remain, however, in using these preparations, the risk of sensitizing the individual to animal proteins and the danger of anaphylactic shock from intravenous injection. Therefore, they are rarely injected by this route. It is possible, however, to inject them intraperitoneally resulting in quite rapid absorption with no more risk of reactions than that from intramuscular injection, as demonstrated by the clinical work of Banks.²

The question not infrequently arises as to whether all patients with scarlet fever should be treated with specific serum therapy, or whether this should be reserved only for the severely ill. This question cannot be answered dogmatically, and undoubtedly there will be a great difference of opinion. Many factors enter into making a decision of this sort.

In general, scarlet fever does not occur in as severe a form today as previously, although occasionally grave forms of the disease still are encountered. Not infrequently, attacks that appear mild at first become severe, and at other times serious complications develop during the course of an otherwise mild scarlet fever. Unless the disease is aborted

by treatment, some toxemia, even in those mildly or moderately ill, will persist on an average of from three to five days

Since the disease can be cut short in its earliest stages by specific serum treatment, and the risk to the patient of the development of a severe form of the disease, of complications and toxemia, can be reduced, it seems logical, though it may not always be practical, to give serum to every patient with scarlet fever, regardless of the severity of the attack

In scarlet fever, hemolytic streptococci cause damage not only by the erythrogenic toxin which they produce, but apparently by other toxins as well, and also by direct invasion of tissues. It has been believed by some that antitoxin for erythrogenic toxin is not always sufficient to produce passive immunity against hemolytic streptococci which cause scarlet fever, since this serum is deficient in bactericidal substances. Passive immunity can be secured for a period of ten days to two weeks with intramuscular injections of convalescent scarlet fever serum when children are accidentally exposed to scarlet fever and there is fear of their developing the disease. Studies have shown that only 1 or 2 per cent of exposed children, who have been passively immunized, will develop scarlet fever, instead of 10 or 15 per cent which can be expected without this prophylactic injection. Those who do develop the disease usually have only a mild or modified scarlet fever.

It was only natural for sulfanilamide to be tried in the treatment of scarlet fever. Unfortunately, the results reported are not as good as those in other streptococcal infections. There is general agreement in the publications that sulfanilamide produces no benefit during the acute, toxic stage of the disease and does not reduce the toxicity nor shorten this stage of the illness.¹¹ Some reports¹²⁻¹³ state that it reduces the likelihood of complications and their severity, whereas in other reports^{11,14} it is stated that even this does not occur.

A word should be said for the combined use of the sulfonamide group of drugs with convalescent scarlet fever serum. It has been shown in a number of experimental investigations in other infections that the sulfonamide group and any specific serum have a synergistic action,^{15,16-17} that is, the combined effect of the two is greater than the sum of the effects of these substances when each is used individually. It is suggested that in patients with severe complications both the drug and serum should be used together.

It has been found that convalescent scarlet fever serum is of con-

siderable value in treating various types of severe hemolytic streptococcal infections in conditions other than scarlet fever. This also has been true in our experience. Benefit has followed the use of convalescent scarlet fever serum where severe streptococcal infections, including blood stream infections, have not yielded to sulfanilamide, or where the patient could no longer tolerate the drug. Out of this experience has arisen the practice of administering both sulfanilamide and serum simultaneously in such serious conditions as streptococcal peritonitis, meningitis, and pneumonia. It is also necessary to give adequate operative treatment of all local sites of infection, such as mastoiditis and osteomyelitis, since serum or sulfanilamide cannot give the best results without essential surgical care of the original or any secondary feeding focus of streptococcal infection.

MEASLES

In recent years the prevention of measles by a number of passively immunizing agents has received increasing attention and use. Whereas there is no direct method of producing a lasting active immunity to measles this can be accomplished to a certain extent indirectly.

The first study in this country of the use of convalescent serum in the prevention of measles was carried out by William H. Park,¹⁸ and as a result of his work and that of others the efficiency of this procedure has been demonstrated in large groups all over the world. In recent years, laboratories have been established in a number of large cities for the preparation and distribution of convalescent measles and other serums.

The blood is obtained from adolescents and adults recently recovered from measles, and at intervals up to four months after the onset of the disease. Serum from thirty or more individual bleedings is pooled and processed as already described.⁶

To obtain maximum protection serum should be injected intramuscularly, if possible, by the fifth day after the child has been accidentally exposed and not later than the seventh. Because this is a human serum, its intramuscular injection is not accompanied by any danger, and local or general reactions are extremely uncommon. When the proper dose of serum is used, the disease will be either prevented or modified in from 98 to 99 per cent of the children, with no measles developing in from 60 to 80 per cent. Failure, i.e., unmodified measles, will occur in from 1 to 2 per cent.

When the disease which develops has been modified, the attack is mild and of short duration, very little if any toxemia is present, the rash is diminished in extent and severity or even absent, Koplik spots are either absent or seen with difficulty, and complications are extremely uncommon. Modified measles may be so mild that it will not be recognized unless one is familiar with it.

An important characteristic of an attack of modified measles is that it confers an active immunity, which persists for years, perhaps for life. This is true if the disease has not been too greatly modified, and for a strong active immunity there must be a detectable eruption. Following some extremely mild attacks of modified measles, after subsequent exposures, some children have developed a second attack of measles, but so far as is known each of these has also been mild.

Convalescent measles serum cannot be standardized at present with any laboratory procedure. Dosage has to be determined by experience.

For prevention, no child or infant should receive less than 5 cc intramuscularly. Our latest information leads us to recommend 10 cc for children from the age of three to ten, 15 cc for older children, and 20 to 40 cc for large adolescents or adults.

Since measles is a serious disease in infants and children up to the age of three (with a mortality rate from complicating pneumonia and other complications of about 5 per cent), we believe that the attempt should be made to prevent the disease completely in exposed individuals of this age group. This should be done also in all exposed children otherwise ill, or recently recovered from an illness, or undernourished. Children in these special categories should receive a somewhat larger amount of serum.

In healthy children five years old or older, it is probably advisable not to attempt to prevent the disease completely, but merely to modify it, in order to secure a permanent active immunity, with very little risk from the mild, modified attack.

For modification half the above doses should be administered up to and including the seventh day of exposure. The full dose given on the eighth or ninth day of exposure at times will modify the disease. After the ninth day of exposure intramuscular injections of this dose cannot be expected to have any effect on the course of the disease.

In hospitals and in children's institutions where exposure to measles has occurred the aim is always for complete prevention of the spread of

secondary cases As already stated, one cannot obtain 100 per cent protection At least a few children will develop modified or occasionally unmodified measles One can prevent, however, general spread of measles, and safeguard against the general development of unmodified measles with its attendant dangerous complications

Other materials have been used in measles prophylaxis Pooled normal serum, obtained from individuals who some time previously have recovered from measles, is efficient when the dose is four times that of convalescent serum Whole blood, obtained from parents or other adults, and injected immediately, is efficient but should be used in eight times the dose of convalescent serum, since serum forms only about one-half the volume of blood The globulin fraction of pooled normal, adult serum or plasma,¹⁹ and of pooled ascites fluid²⁰ and the placental globulin fraction in corresponding doses,²¹ have proved to be efficient

Formerly, it was thought that since measles is a virus disease, once its earliest manifestations had developed, it would be impossible to modify its course by the therapeutic use of serum At the Willard Parker Hospital, New York, Kohn, Klein and Schwarz²² demonstrated that 50 cc of convalescent measles serum administered intravenously to children who are in the pre-eruptive stage of measles, showing Koplik spots, will mitigate the disease in about 85 per cent (25 children treated), so that, in brief, the resulting disease may be characterized as a mild, one-day illness Similar results were reported by Levinson and Conner²³ at the annual meeting of the American Academy of Pediatrics in 1938 The importance of such observations is that many children already seriously ill with diphtheria or poliomyelitis, for example, who are discovered to be developing measles, can be spared the added risk of a severe attack of the unmodified disease

About the treatment of measles after it has reached the eruptive stage, which should be the main topic in this section, not very much can be said There has been no clear-cut evidence presented that once the eruption has appeared, convalescent serum will produce any demonstrable benefit None of the publications seems convincing, and in light of the results described above of treatment in the pre-eruptive stage, one could not expect benefit from the comparatively small doses mentioned in the reports of treatment of active measles We do not recommend the use of convalescent serum after the eruption has appeared

CHICKEN POX

Convalescent chicken pox serum has been used in an attempt to prevent this disease, and also therapeutically. Unfortunately, the experience of others and the trial at the Willard Parker Hospital indicate no efficiency in either prevention or treatment.

DIPHTHERIA

Active immunization against diphtheria is so simple and has proved so successful that diphtheria must be considered today a preventable disease.

The treatment of active diphtheria, when it does develop today, is practically the same as it was after diphtheria antitoxin became generally available, except that better, more refined and safer antitoxic serums are now generally available.

In the opinion of many, diphtheria is going through a cycle of decreasing severity. Whether diphtheria goes through these natural cycles, or whether widespread active immunization, better hygienic conditions or other factors are responsible, is not clear. Even today occasional cases of severe or malignant diphtheria occur. It is particularly imperative that serum should be administered as early as possible, and in sufficient amount in one dose. Enough serum administered early is much more valuable than larger amounts given later in divided doses. In severe attacks of laryngeal or malignant diphtheria, part or all of the serum should be given intravenously, unless the individual is sensitive to horse serum when the injection should be made intraperitoneally, absorption being much more rapid than by the intramuscular route.

The minimum dose in an early attack of faucial diphtheria of average severity is 10,000 units intramuscularly. Large or older children should receive more, and individuals with the severest form of the disease should receive 40,000 to 60,000 units of antitoxin, all of it or half of it intravenously.

In recent years, Ramon^{24, 25} and his co-workers have been using and recommending a type of therapy which they call sero-antiotherapy, meaning combined therapy with antitoxin and toxoid (anatoxin). They claim for this method that it does not decrease the curative effect of the antitoxin and that active immunity is stimulated by the toxoid sooner and more certainly than it would otherwise occur, minimizing complications and the frequency of relapse. This work is of extreme interest and

should be followed further. There is some evidence, from animal experiments, of a contrary nature, but this, as claimed by Ramon, might not apply to humans.

TETANUS

Much more progress has been made in recent years in the active immunization against tetanus than in passive immunization or in treatment of the active disease.

Ramon and his group^{26, 27, 28} were the first to produce tetanus toxoid, and demonstrated its efficiency in animals and humans as an agent for causing a strong, durable, active immunization. Their work has been verified by many others and extended in some directions.

The production of tetanus antitoxin after a single injection of tetanus toxoid is slower than after an injection of diphtheria toxoid. It has been found that one injection is not sufficient to produce the desired response and that the spacing of the injections must be different from those with diphtheria toxoid. The second injection should be given not sooner than one month after the first. The immunity which develops does not reach the highest possible level but, nevertheless, persists for about a year. When an additional injection of toxoid is administered a year after the first one (this is called a secondary or a recall injection), it is then found that the antitoxin rapidly reaches a comparatively high level. The same level of antitoxin in animals will protect them from at least one minimal lethal dose of tetanus toxin, and will protect most, if not all of the animals, from at least one minimal lethal dose of tetanus spores injected intramuscularly.

Because of these results active immunization to tetanus is being more and more extensively practiced in some of the European armies (France and Great Britain), and for individuals whose work exposes them intimately to the likelihood of tetanus infection. Its use in civil practice seems to be spreading gradually, also.

How efficient this active immunization is or has been in the prevention of tetanus in wounded and injured individuals in the present European war, so far as can be learned, has not been reported.* This infor-

* Since this paper was written Perry²⁹ reported in the *British Medical Journal*, that compared with the first three months of the war of 1914-18, when the incidence was about 8 per 1,000 wounded, the figure in the war is 0.45 per 1,000. It is significant that such cases as have been noted have occurred in individuals that have not been actively immunized. Among casualties of the British Expeditionary Force there has been no reported instance of tetanus in soldiers protected by means of tetanus toxoid. It is only fair to remark that a number of wounded received prophylactic doses of tetanus antitoxin subsequent to their arrival in this country—that is to say, two or three days after the infliction of the wound.

mation will be awaited with the greatest of interest

Until this information is available, the question which is most frequently asked is If an immunized individual (soldier or civilian) receives a wound or injury from which experience has shown tetanus is likely to develop, should the active immunity alone be relied on or should additional methods of protection be used immediately after the injury? Until more is known about this, the prevailing opinion at present seems to be that an intramuscular injection of tetanus toxoid should be given as soon as possible. It has been shown that this additional dose of toxoid will stimulate the rapid increase in tetanus antitoxin in from five to seven days, an interval which is sufficient to prevent tetanus, since it usually takes five or more days for tetanus spores to germinate, disseminate toxin, and produce the disease.

If animals previously immunized with tetanus toxoid are injected with a mixture of tetanus spores and calcium chloride, an increase in the antitoxic titer in their blood occurs slowly, if at all, and apparently only those animals survive which have a sufficient active immunity at the time of the spore injection. However, if tetanus toxoid is injected in a different muscle at the same time that the spore-calcium chloride mixture is injected, in from five to seven days a definite increase in the level of antitoxin in the blood is found and a larger percentage of animals survive. The exact level of antitoxin necessary to protect against spore injection is not known but is believed to be larger than that needed to protect against tetanus toxin.

The prevention of tetanus in injured, non-immunized individuals remains a problem. Experience in the last war demonstrated that a single injection of 1500 units of tetanus antitoxin is not sufficient. At times this will only delay the onset of tetanus which may develop weeks or months later. Tetanus was controlled best when repeated injections of antitoxin were administered at 10-day intervals for as long as seemed indicated by the condition of the wound.

At present, Ramon^{30, 31} suggests that the wounded non-immunes should receive both tetanus toxoid and antitoxin so as to have the benefit of both active and passive immunization, since his animal experiments indicate that the administration of antitoxin does not slow up the process of active immunization from the toxoid. However, experimental work by Otten and Hennemann³² leads them to conclude that the injection of antitoxin does slow up the development of active immunity from

toxoid They suggest that antitoxin should be administered immediately for passive immunization, and an injection of toxoid be given as well These should be followed by several injections of antitoxin and toxoid at intervals of about ten days, sufficient to maintain by passive immunization a protective level of antitoxin until active immunization will maintain this level

Sneath and his co-workers³³ have investigated the relative degree of protection in guinea pigs by active and passive immunization against infection from the injection of standardized doses of tetanus spores mixed with calcium chloride solution A larger number of actively immunized guinea pigs survived and were completely protected from tetanus when their blood contained 1/100 unit or more of tetanus antitoxin per cubic centimeter, than unimmunized guinea pigs which received the passive immunizing dose for humans of 1500 units of antitoxin, a huge dose for these small animals The explanation of the difference in the experimental results with passive immunization in guinea pigs and those in man is not clear, but indicates that further studies should be made in man

In civil practice there are certain disadvantages, such as reactions, serum sickness, and sensitization, to the administration of a prophylactic dose of tetanus antitoxin to children who have received comparatively trivial puncture wounds, and yet it is a serious responsibility for a physician to deny the child protection against tetanus

Since the campaign for active immunization with tetanus toxoid has spread it has been found that some adults develop a relatively high titer of antitoxin in their blood, 10 units per cubic centimeter being not uncommon, with occasionally as much as 50 units

Several years ago Schick suggested to me the preparation of human tetanus antitoxin for prophylaxis for just those instances when the physician hesitates to use an animal antitoxin This suggestion has also been made by Hyland, as reported by Dietrich³⁴ Unfortunately, it was impossible for me to secure blood from humans actively immunized and with a sufficiently high titer of antitoxin However, should all members of the American army now being formed be immunized with tetanus toxoid, it should be possible to obtain large amounts of tetanus antitoxin (human), and it is hoped that someone will determine how efficient this antitoxin will be

Definite advances have been made in recent years in the treatment of tetanus, once it manifests itself This has been excellently described

and summarized in two recent articles by Dietrich³⁴ and Spaeth³⁵ and also by Vener and Bower³⁶ These workers advise that an initial large dose of antitoxin be administered, preferably by the intravenous route in spite of the risk Spaeth believes that one dose, if large enough, is sufficient Dietrich believes that repeated intramuscular injections should be given also, so as to maintain a high level of circulating antitoxin Since resistant spores may continue to germinate and produce toxin after the initially injected antitoxin has disappeared, repeated injections are logical Both of these investigators agree that it is of the utmost importance to keep the patient as quiet as possible under a regime carried out by a specially trained personnel, to administer sedatives cautiously, but in sufficient amounts to prevent convulsions, to avoid all manipulations and unnecessary physical examinations if possible, to administer sufficient fluids and nourishment and not to perform lumbar punctures or administer serum intrathecally They believe that the intrathecal administration of serum causes meningeal irritation which is harmful and that the anesthesia necessary for lumbar puncture is also harmful Both believe that deaths have been caused by excessive serum treatment and overmanipulation Apparently overtreatment must be avoided, nevertheless, large amounts of antitoxin must be administered

The importance of preventing convulsions with sedatives, aside from the exhaustion which these cause the patient, is graphically illustrated by the reply of one child who recovered when he was asked how the convulsion felt, he said, "You know how much it hurts when you have a cramp in your leg Well, convulsions feel like that all over"

It is difficult to make a comparative evaluation of results in the treatment of tetanus, but certainly those reported by these investigators seem excellent and give hope that they can be repeated or even improved

BACTERIOPHAGE

When it was discovered that bacteriophage would cause solution and death of bacteria *in vitro* it was hoped that this could be accomplished *in vivo* Unfortunately, the clinical trial of many types of bacteriophage has been disappointing Therefore, bacteriophage is very seldom used today in the treatment of bacterial infections a further indication of its lack of efficiency

Each phage has a specific range of activity and as would be ex-

pected, the least efficiency is found in stock preparations. It requires several days for trained workers to prepare a specific phage, during the time when the need of treatment is most urgent. Only actively growing bacteria are lysed, resistant strains are not uncommon, and will develop if lysis is incomplete. Proteins and many other colloids inhibit lysis and inflamed areas are walled off, reducing the probability of contact of phage and bacteria. The injection of bacterial filtrates may cause a therapeutic response similar to phage. Preparations of bacteriophage contain peptones, meat extracts, products of bacterial growth and dissolved bacteria, all of which may cause physiological effects or systemic reactions.

In general blood stream infections, bacteriophage has been given intravenously by some. The initial doses must be very small, about one-tenth of a cubic centimeter, and severe, febrile and chill reactions are caused not infrequently. Gradually increasing doses are administered at intervals of several hours, and reactions may occur after any of these. Some investigators have believed that beneficial effect will follow only when reactions of this sort have been produced, and others are of the opinion that the improvement which occurs should be attributed not to the phage but to a general, non-specific reaction.

Extensive use of phage in the treatment of severe staphylococcus infections, including bacteriemia, has been made by MacNeal and his colleagues.³⁷ They are convinced that much has been accomplished in the treatment of a large series of patients. Although statistical evaluation is difficult, the favorable opinion of such outstanding workers must be given serious consideration.

With the recent development and use of chemotherapy in bacterial infections it will be more difficult than ever to estimate the value of bacteriophage in staphylococcus infections.

It is questionable, from the published reports, if phage has any efficacy in the treatment of bacillary dysentery.

STAPHYLOCOCCAL INFECTIONS

Until the recent use of sulfathiazole, one had to rely on bacteriophage, antitoxic serum and multiple small blood transfusions in the treatment of severe staphylococcus infections with or without bacteriemia. Apparently the antitoxin as developed by Dolman^{38, 39} and by Ramon⁴⁰ has been of real help in treating some patients. Perhaps, under desperate

circumstances, a combination of sulfathiazole and antitoxin should be used, as it is logical to believe that these two will act synergistically, as do other similar combinations

There is some evidence^{41, 42} also, that multiple injections of staphylococcus toxoid are beneficial in the treatment of even severe acute infections. Not all observers agree about this. The beneficial results of the treatment of subacute or chronic staphylococcus infections with toxoid seem more clear-cut but here, too, there is not complete agreement of different investigators. The best results seem to be in the prevention of recurring attacks of boils by the injection of toxoid during the intervals between these attacks. Autogenous staphylococcus vaccines have a limited efficiency under these conditions, also

GAS BACILLUS INFECTIONS

As pointed out in a recent editorial in the *Lancet*,⁴³ the treatment of gas gangrene with antitoxin appears to have fallen in disrepute for reasons that are difficult to find. During the last war there can be little doubt that the lives of many individuals infected with *Clostridium welchii* and *Vibrio septique* were saved by means of antitoxic sera of low potency as compared with those produced today. This efficacy was both prophylactic as well as therapeutic. Since then this experience has not been much enlarged, if for no other reason, because of the infrequent occurrence of gas gangrene in civil practice.

Although more recently some excellent therapeutic results have been achieved with the use of the sulfanilamide group of drugs it would be unfortunate if an attempt were not made to improve upon these results by the use also of modern, potent sera. This is especially important since recently Henderson and Gorer⁴⁴ have demonstrated experimentally in animals infected with the organisms of gas gangrene that "there is a striking, synergistic curative action of sulfapyridine plus antitoxin." Their study indicates that in treating the disease in humans an adequate dose of antitoxin should be given intravenously at the earliest possible moment, one therapeutic dose for the suspected case, and for the established case, three to five doses combined with 6 to 9 grams of sulfapyridine daily until the infection is obviously controlled.

ANTHRAX

Anthrax is so uncommon in this country that unfortunately infec-

tions of the skin caused by this organism are not always recognized immediately. Early diagnosis is of extreme importance for successful treatment, as the disease frequently reaches the bacteriemic stage with great rapidity.

After many kinds of treatment of the local skin lesion, such as, excision, cauterization with chemicals, or the actual cautery, it is now generally agreed that the lesion should merely be protected and kept dry, as manipulations tend to spread the infection rather than control it.

Anthrax antiserum should be administered intravenously at the earliest possible moment in large amounts of 100 or 200 cc at a time, after, of course, taking the usual precautions against sensitivity of the patient to the animal serum. Large injections should be repeated intravenously once or twice during the first twenty-four hours, and continued at intervals for several days until definite improvement or recovery has occurred. All observers have not obtained equally good results, but certainly some recoveries seem attributable to early, vigorous treatment.

BOTULISM

Although this condition is relatively uncommon in this country, it still occurs occasionally in outbreaks in small or large groups who have eaten foods containing the toxin of *Clostridium botulinum*. Under these circumstances the disease has a high mortality.

In 1934 Velikanov and Kolesnikova⁴⁵ reported an excellent clinical study of 227 cases of botulism. Of these, 146 received serum, and 81 that did not served as controls. Among the 146 that were treated, 26 died, a mortality of 18 per cent, and among the 81 not treated with serum, 76 died, a mortality of 93 per cent.

Large amounts of serum were given, each dose being from 60 to 100 cc. The best results were obtained when this treatment was given early in the disease.

Some of the most severely ill received repeated doses of serum at short intervals, a few as much as a total of 600 to 700 cc.

In several apparently hopeless cases serum was administered intravenously, and twice intraspinally in doses of 10 to 20 cc with recoveries that were described as astonishing.

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INFECTIONS OF THE MIDDLE EAR AND NASAL SINUSES *

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WHEN it is realized that every cold is a potential sinus involvement and that chronic sinusitis probably causes more ill-health than any other disease, it is obvious that every physician should be thoroughly familiar with the pathological changes which accompany sinusitis. The general physician is the first to be consulted, he should, therefore, be in a position to give authoritative advice. Yet, in the past, comparatively little has been known about the physiology of the nose, the pathology of sinus infection, the effect of constitutional conditions upon the function of the nose, and the possibility of allergic influence has not always been sufficiently considered.

ANATOMY AND PHYSIOLOGY

The nose is an extremely complicated anatomical structure. No two nasal chambers are exactly alike, no two can be expected to act alike, even in the same individual. Nor do any two patients respond identically, either constitutionally or locally, to nasal therapy.¹ The function of the nose is so controlled through the nervous system that any abnormality in any portion of the body, from the skin to the heart, may have a decided bearing on it.

Small wonder, then, that there is considerable confusion on the subject in the mind of the layman, the general practitioner and even the rhinologist. I believe Ballance has well stated the case when he says, "Once the pathology is understood, differences of opinion as to therapy should disappear."² To further this better understanding, let us briefly review some of the high lights in the anatomy and physiology of the nose.

Chambers The nose consists of two chambers separated by the septum and surrounded by cavities connected with it by very small open-

* Given October 21, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

ings, called ostia, which render the passage of air from the nose into the sinus and drainage from the sinus possible

Turbينات There are three turbinate bodies situated one above the other in the lateral wall of each chamber, dividing this wall into three compartments called respectively the superior, middle and inferior meatus. The turbinates have the most abundant blood supply of any part of the nose, they have much elastic and smooth muscle fiber and large cavernous sinuses, giving them the characteristics of erectile tissue and rendering them particularly responsive to all types of sympathetic nervous system reactions, to inflammation or allergies, to thermal, chemical (either local or general), emotional and constitutional changes. Their function is to direct properly, warm and moisten the inspired air. Because this function is maintained by the coordinated action of both sensory and involuntary nerves, any constitutional dyscrasia may cause functional nasal changes and local symptoms which may simulate sinus disease. "Such symptoms as nasal obstruction in hot dry rooms, a watery discharge in cold weather, and, during adolescence, the dropping back into the throat of secretions and the obstruction of the nose on the dependent side are physiological responses which need not necessarily be the result of pathology in the nose."³ It is well to look for causes other than nasal, when the patient complains of a postnasal discharge which is not excessive, especially where there is no pronounced tracheal cough. Fifty per cent of such cases are probably allergic. Other possible causes are endocrine imbalance, intestinal stases, anemia, syphilis and diabetes. When the postnasal discharge is abundant and accompanied by the characteristic tracheal cough, the cause is usually sinus infection. As the turbinates are important in directing the air currents to the nasopharynx, due consideration must be given these facts where operative interference is contemplated.

Position of Ostia—Inferior Meatus The lacrimal duct empties into the inferior meatus (below the inferior turbinate), hence the futility of treating nasal conditions with drops put into the eye.

Middle Meatus Into the middle meatus (below the middle turbinate) empty most of the sinuses, i.e., the antra, frontals and anterior ethmoids, therefore, the anatomy of the middle meatus is the most important insofar as sinus involvement is concerned. Drainage from all sinuses depends principally on ciliary action. The frontal sinus drains *down-hill* from its lowest point by a long, often tortuous, passage

through the ethmoids into the middle meatus. The anterior ethmoids drain *down-hill* into the middle meatus at nearly the same point as the frontal and antrum. The antra empty into the middle meatus through one or more openings situated in the uppermost part of the antral cavity, necessitating *up-hill* drainage. Here any interference with the action of the cilia renders drainage impossible.

Superior Meatus The posterior ethmoids empty into the superior meatus (below the superior turbinate), while the sphenoid empties into the space above and posterior to the superior turbinate. The sphenoid is drained by an opening situated high on its anterior surface, necessitating *up-hill* drainage, here, too, the action of the cilia is of prime importance.

It is thus evident that all the sinuses drain down-hill excepting the antrum and sphenoid. The antrum is the most common site of infection, the sphenoid the rarest. The probable explanation is that the anatomical structures surrounding the ostia of the antrum are far more liable to be deformed, thus obstructing the ostia and impeding ciliary action. For this reason the antrum is the sinus most likely to require aid to drainage.

Drainage A large part of the drainage from the sphenoids and posterior ethmoids goes down the throat. Most of the other sinuses, by reason of ciliary action, would naturally drain down the throat also, but the action of blowing the nose directs a certain amount anteriorly. The post-nasal and the lymphatic drainage from an infected sinus causes the tracheal cough so characteristic of sinus infection.

Causes of Ostial Obstruction If the formation of the nose were perfect, sinus infection would occur only as a result of swimming, ill-advised local applications or allergy. Since such perfection is rarely attained, we shall find that about 85 per cent of all x-rays of the nasal sinuses show some degree of involvement. A septal ridge or spur which projects into the middle meatus, especially in the anterior part crowding the middle turbinate against the outer wall and so interfering with the function of the ostium of the antrum and other sinuses, is almost certain to result in poor drainage from these sinuses with consequent chronic infection. When there is obstruction of one side of the nose by a deviated septum, there will be a compensating enlargement of the turbinate on the opposite side as a result of improper aeration. A middle turbinate which has become greatly enlarged as a result of improper aeration, a misplaced ethmoid cell or persistent allergic reaction will most certainly obstruct

the ostia by its size alone, and sooner or later infection will occur. In such a case, it is necessary either to relieve the underlying allergy, improve air circulation or create better drainage for the sinuses involved.

Respiration When the nasal ostia are unobstructed, inspiration causes a negative pressure in the nose and sinuses, expiration, a positive pressure. It has been demonstrated that when, because of obstruction of the ostia, pressure in the nose and antra differs, secretion will generally be found in the antra. Insufficient ventilation of the nose, with the resultant mouth-breathing, also causes poor drainage from the sinuses.

Absorption Experimentally, it has been shown that dyes placed in an acutely inflamed sinus, of which the ostia are completely blocked, will appear in the urine within fifteen minutes. This will give some idea of the absorbing power of the mucous membrane in inflamed sinuses when the ostia are blocked by acute swelling or chronic thickening. It also explains why the sinus patient seems more ill than one with an ordinary cold.

Cilia The cilia constitute the greatest protection which the nose possesses. The entire lining membrane of the nose and sinuses is supplied with these hair-like processes which wave toward the ostia and the nasopharynx. Over the cilia is a tenacious layer of mucus which tends to catch foreign particles and invading bacteria and is moved onward by the cilia. The introduction into the nose of anything which interferes with the ciliary action or the mucous coat, impairs the natural protection supplied by the mucous membrane. For this reason the habit of spraying the nose with antiseptics is obviously not to be recommended. Unobstructed ostia and free ciliary action are all-important and must be maintained or reestablished at all times. In acute infections, swelling of the membrane in the ostia halts normal drainage, hence, anything which tends to shrink this membrane is an advantage. Our choice of drugs—of which we shall speak later—must be confined to those which do not interfere with ciliary action. Thick pus retards or stops the action of the cilia, and should be evacuated by means of lavage. Since ciliary action ceases at temperatures below 53° and above 109°F , the use of too hot or too cold solutions or vapors is contraindicated.

Allergy In any nasal syndrome, allergy must first be considered as a possible cause. Hansel gives statistics indicating that in about one-third of the cases seen by the rhinologist, the symptoms are primarily allergic.⁴ Such cases can usually be determined by a careful preliminary history.

Negative skin tests cannot always be accepted as ruling out any sensitivity. When allergy is the underlying but undiscovered cause, the result of any and all nasal procedures is likely to be unsatisfactory, and it will explain many disappointing results of surgery. Allergy can simulate every nasal symptom of which a patient may complain. He may have what he calls a "cold," although a careful history will reveal that these "colds" come suddenly, with sneezing and are of but one or two days' duration, or he may have a "chronic cold" which strongly suggests sinusitis but may actually be allergic. Any medication in a nose of this type is likely to increase the symptoms. Operations are contraindicated unless the allergy is also treated, many nasal operations would prove unnecessary if the underlying allergy were treated first. On the other hand, the perennial types of allergy may bring about permanent changes in nasal membranes rendering them more susceptible to infection, here operation for the cure of infection should be undertaken. In cases where treatment of the allergy, per se, fails to give adequate relief, the removal of hypertrophied tissue will help, by improving drainage and ventilation.

Now that we have an up-to-date outline of the physiology and pathology of the nose and nasal sinuses, let us consider briefly the pathology and treatment.

Pathology If the function of the nose is unimpaired, a "cold" is self-limited and will disappear in a few days. If the symptoms are due to an allergic condition, it will clear up in one or two days unless there is a superimposed infection or too much medication to which the patient is sensitive. A cold which persists longer than a week, with continued congestion of one or both nostrils, excessive secretion, cough or recurring temperature, with or without pain, is strongly suggestive of sinus involvement. At the beginning of a cold, there is an acute congestion of all nasal membranes, the ostia swell and drainage becomes difficult. At this point anything that can be done to improve the general resistance and open the nasal ostia by shrinkage will facilitate prompt recovery. When, in spite of all efforts, the ostia do not open, suppuration follows. If this stage is prolonged by failure to aid drainage by lavage through the normal opening, there is infiltration of the connective tissue and permanent hyperplasia of the lining membrane. Unless drainage is now obtained, degeneration of the mucosa together with polypoid and cystic formation occurs. This condition can be cured only by removal of the diseased tissue, if this is not done, the patient must tolerate the symptoms.

of chronic sinusitis. Hence the importance of recognizing the symptoms of acute sinusitis and of not allowing them to become chronic.

Antra My personal experience has led me to believe that the antrum is the keystone to most nasal pathology and the best point of attack. In support of this thesis, I present the following statistics obtained from a cross section of one thousand case histories taken from my private practice. These histories cover a twenty-five year period, limited to ear, nose and throat work, and are drawn from approximately twenty-thousand records. Of the thousand cases studied, 474, or 47 per cent, gave no history of nasal disturbance, the remaining 526, or 53 per cent, showed nasal involvement in the following proportions:

191, or 36 per cent were due to causes other than sinus infection

335, or 64 per cent, were due to sinus infection

The distribution of these 335 cases is shown in Table "B"

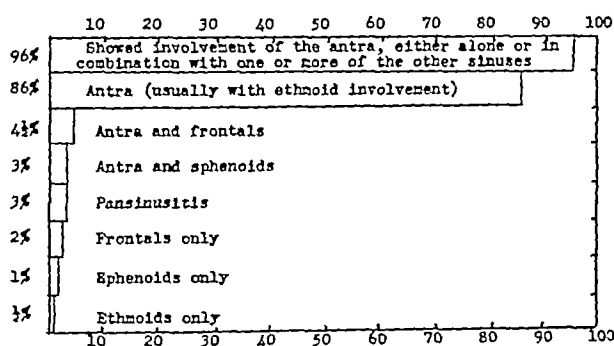


TABLE "B"
Chart Showing The Incidence of the
Involvement of the Various Sinuses

From these statistics the importance of the antra as retainers of nasal infection appears self-evident. Granting this, it is also evident that if acute antral infection is prevented from becoming chronic there will be far less involvement of the other sinuses through extension of infection. The above figures show how rarely the ethmoids are involved without accompanying involvement of the antra, and vice versa. In such combined infections, whether acute or chronic, treatment of the antra will do much to clear up the ethmoids but treatment of the ethmoids will never cure the antra.

Because of the anatomy of the nasal chambers, treatment of the antra will almost always tend to clear up any other sinuses simultaneously involved. In the acute stage, shrinkage of the middle meatus is advisable, this can be done by means of a pledget of cotton moistened

with a mild cocaine solution, and the use of ephedrin (1 per cent) in normal saline in the form of drops. As the acute stage passes and the secretions become thicker, it is advisable to aid drainage by lavage of any obstructed sinus. Such lavage can best be accomplished, with the minimum of trauma, by passing a cannula through the normal or accessory opening. In the chronic stage of pansinusitis, operation on the antra will do more to clear up the other sinuses than any other procedure.

Medication A wide variety of drugs has been tried in nasal treatment and experience has taught some very important lessons in this field.

Dilute ephedrin, a one per cent solution in normal saline, interferes as little as any known substance with the natural function of the mucous membrane. It is excellent to relieve congestion and to assist sinus drainage. It should be used, without preservatives of any kind, in the form of drops (one-half inch of the solution in an eye dropper) placed in each nostril with the head well back. It should not be used too frequently, as some patients develop an intolerance for this drug. Increased congestion following its use indicates either the existence of such an intolerance or of a sinus which needs attention.

Benzedrine inhalant will give considerable temporary relief but used too frequently will produce bad constitutional reactions. It has, however, no effect on the cilia.

Cocaine in a weak solution (not over 5 per cent) has no deleterious effect upon the cilia. In the majority of cases its use by direct application, alone or in combination with ephedrin, is most effective in shrinking the ostia. However, inquiry should always be made regarding the patient's reaction following its use, since cocaine may cause severe headache and depression and some people have a decided idiosyncrasy for it. Whenever a patient reports headache or malaise following treatment, the cocaine is sure to be the cause. In all such cases, a substitute, such as pantocaine (2 per cent) and ephedrin (1 per cent) should be used.

Normal salt solution does not interfere with ciliary action but the habit of daily irrigation with this solution will in time produce definite changes in the mucous membrane. It is also well to note that after nasal operations dry treatment is preferable to wet, as moisture causes edema of the new tissue.

Argyrol and neosilvol used frequently, or over an extended period, will produce argyria. Patients often exhibit the characteristic silvery,

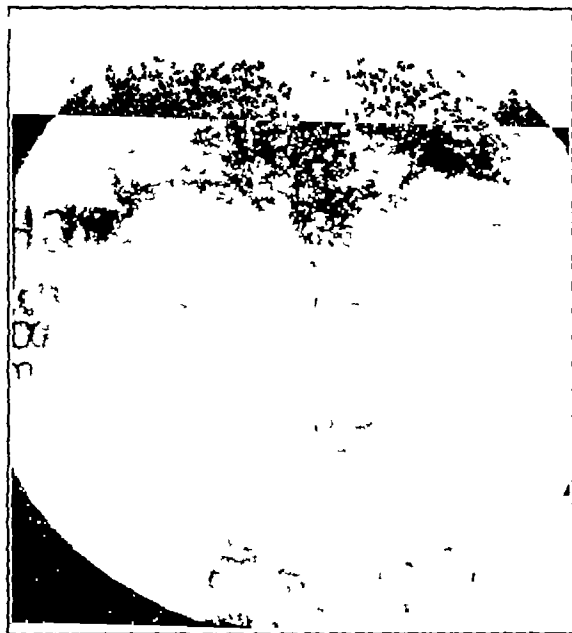


Figure 1 A case of chronic pansinusitis before treatment



Figure 2 After treatment the same patient as Figure 1, 15 months after double radical operation on the antra showing the beneficial effects on the other sinuses

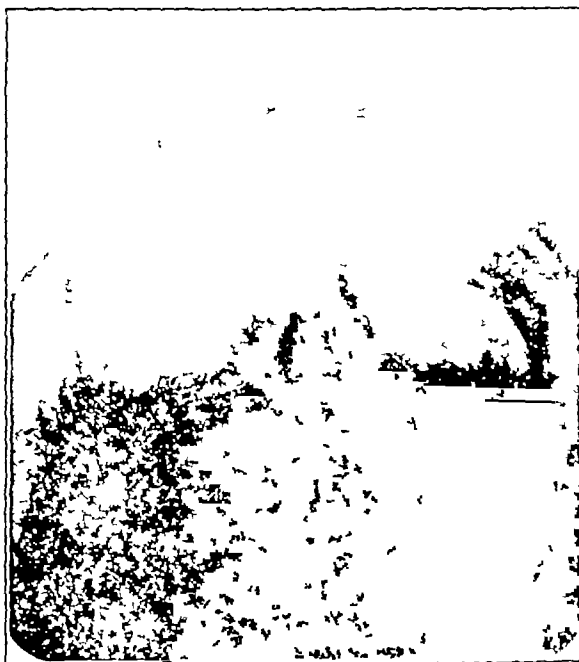


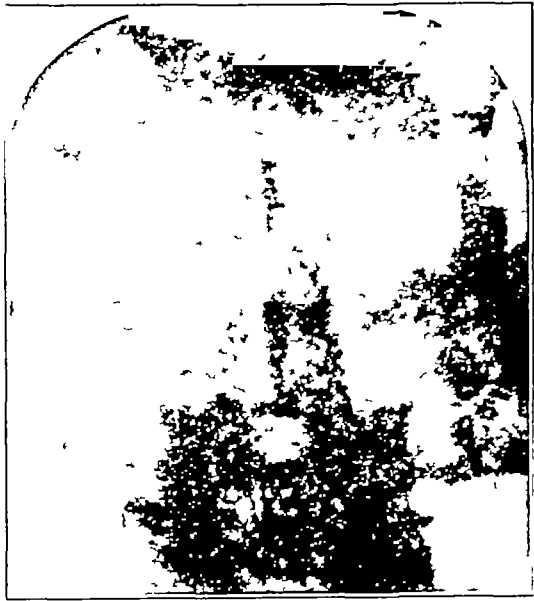
Figure 3 Before treatment an acute pansinusitis which was cured in three weeks by lavage through the normal openings, four drachms of thick pus were originally found in each antrum



Figure 4 After treatment the same patient as Figure 3, two months later, showing that the antra cleared



Before



After

Figures 5 and 6 The same patient as Figure 3, showing that the ethmoids and frontals cleared after treating the antra



Before



After

Figures 7 and 8 The same patient as Figure 3, showing that the sphenoids cleared after treatment of the antra

dusky skin, black turbinates and nasopharynx, black streaks down the pharynx (I have seen the interior of the larynx black) following the prolonged use of argyrol. The appearance of argyria may possibly be delayed months after the drug is discontinued but once it appears it is permanent. Since argyrol has no bactericidal properties when used in a pack, any beneficial result obtained is due to osmosis. In other words, the patient's nose is washed in its own secretions and shrinkage is obtained by drawing fluids out of the tissue. Hypertonic saline solution would accomplish the same result without danger of argyria.

Petrolatum does not interfere with ciliary action but it lies on the mucous coat and by its additional weight slows the progress of this coat toward the nasopharynx. This is true of any oily solution. It has been shown that drugs dissolved in oil do not penetrate the mucous coat to reach the epithelium, phenol and iodine are so firmly held in oil that they are rendered inert. Mineral oils when used in the nose have been known to produce lipoid pneumonia, especially in children, vegetable oils are less harmful. As a matter of fact, oil should be used only in chronic crusting conditions where the cilia are not functioning.

The constant use of any of the popular sprays for the nose, containing menthol, eucalyptol, camphor, petrolatum, will produce definite changes throughout all layers of the mucosa and is not to be recommended.

X-ray treatment of sinusitis is still debatable, some men claim excellent results in the acute stages of infection. The literature does not confirm this.

Diathermy is reported to cure when used twice a week for a month, but I have seen it increase the pain in acute frontal sinusitis, and no confirming articles on the subject have appeared in the literature.

Many other treatments have been advocated for use daily, or twice weekly, with the claim that cases so treated recover in a month's time. One cannot help echoing Hoople's question whether "these treatments do not prolong the condition to make it last so long."

Chemotherapy in nasal pathology Recently chemotherapy has entered the field of nasal therapy but so far there is very little to be found in the literature on the subject of its use in sinus infection.

I have used chemotherapy on very severe aural and nasal infections, which seemed to be getting out of control and the result has been miraculous. I, personally, have not seen, in the treatment of sinusitis, any

flare-ups following the discontinuance of the drug, such as frequently occur in mastoiditis. However, at the recent American Medical Association meeting in New York City, Dr. Shambaugh reported two patients on whom chemotherapy was used, who apparently recovered, yet later developed meningitis and died. To my mind, this report constitutes a warning rather than a contraindication to the use of the drug. I have also tried chemotherapy on cases of chronic nature, with thick pus in the antral washings and thickened membrane in the sinuses, in these cases I have had very negative results. Apparently the drug works best, in sinusitis, in the presence of a fulminating infection. According to Shambaugh's report, it may have a masking effect, just as in mastoiditis, and will therefore need careful watching even after the patient is clinically well. The best method of checking on this masking effect is by means of x-rays. I have seen patients, clinically recovered from mastoiditis and frontal sinus infection whose x-rays showed progress in bone destruction. It is safer, in the presence of an undrained focus of infection, not to rely too much on chemotherapy alone.

Chemotherapy in aural pathology "My experience leads to the conclusion that chemotherapy is of decided advantage in the treatment of acute purulent otitis media provided it is started early before the condition of the mastoid has progressed to softening of the bone. Where such softening has occurred, the use of chemotherapy so changes the clinical picture as to make it almost impossible to determine the presence of progressive bone destruction and to ascertain the advisability of operating. With chemotherapy the clinical picture has ceased to be the reliable guide to pathological conditions in the mastoid, and roentgenograms have become an invaluable aid and at times afford the only diagnostic sign. In doubtful cases it is well to stop administration of the drug for a time in order to get the true clinical picture.

Chemotherapy is indicated if, at the time of myringotomy, the fundus has a very bad appearance or if myringotomy reveals pus or fluid under great pressure, with or without the presence of mastoid tenderness and regardless of the results of culture.

If the fundus does not seem to be in bad condition and the pressure on myringotomy is not great, chemotherapy may be deferred, but, if subsequently the ear does not improve promptly, chemotherapy should be started at once, regardless of the culture. If complications intervene, the drug should be used immediately regardless of culture,

but never without removing the focus

After mastoidectomy the wound should be free from pus and the temperature should return to normal within two or three days. If chemotherapy is given during this early postoperative period and if it produces persistent temperature accompanied by symptoms simulating meningitis or labyrinthitis, the picture is very alarming. For this reason, it is preferable *not* to give the drug postoperatively in *uncomplicated* acute mastoiditis.

The drug is not effective in uncomplicated *chronic* mastoiditis. Its efficiency is lessened in cases in which there have been previous severe attacks of acute purulent otitis in the same ear.

From a series of 793 cases of acute purulent otitis media, treated during the past three years, 50 per cent of whom were given chemotherapy, I draw the following conclusions:

If chemotherapy is given early before bone destruction occurs, the duration of discharge and the number of mastoidectomies is diminished by about 50 per cent.

When the clinical picture strongly suggests mastoidectomy, it is safer to operate.

After uncomplicated mastoidectomy, it is better *not* to give the drug.

Complicated mastoiditis requires intensive chemotherapy.

At times it is necessary to stop the drug in order to obtain the true picture, as the middle ear may respond favorably to the drug while progressive bone destruction is taking place in the mastoid."⁶

Sulfathiazole should *not* be used in meningitis secondary to ear, nose and throat infections as it is not absorbed into the spinal fluid.

A general rule to follow in the administration of the drug is that when there is no response in 48 hours to chemotherapy *properly given*, some additional help must be obtained. One of the apparent causes for failure of chemotherapy in such cases, is lack of development of antibacterial antibodies on the part of the host. However, when indicated, antibody determination can be made.⁷ The administration of the drug may be stopped or delayed for a few days, to allow time for the formation of antibodies but this will not be found as satisfactory as the use of immune sera and immuno-transfusions. Any one of these, or a combination, may be sufficient to insure the successful increase of antibacterial antibodies and therefore a better response to the drug.⁷

Of the various forms of the drug in present use, sulfanilamide appears to be specific for the *Streptococcus hemolyticus*. Sulfapyridine has a broader usefulness, it is efficacious in pneumococcic and in staphylococcic infections as well as in streptococcic. It may produce toxic symptoms which are often severe, sometimes simulating meningitis so closely as to be alarming when it is used in the therapy of nose and ear infections. It should, despite this, be used in true meningitis. Sulfathiazole, although it frequently causes rashes, seems to be less generally toxic, it has an excellent effect on pneumococci, streptococci and staphylococci. If the drug is used, it should be given in sufficient quantities to produce results or not at all. If the patient does not respond to one form of the drug, it is well to substitute one of the others. Our general rule for dosage is to give during the twenty-four hour period an amount totaling slightly less than one grain (0.06 gm) per pound of body weight up to 90 pounds (41 kg). During the first twenty-four hour period, we double, triple or quadruple the amount for the first two or three doses, depending on the severity of the infection and the type of patient. It is, of course, essential to watch the urine and blood carefully. At first a daily blood count is taken, later, if no bad effects are observed, the interval is lengthened to once in two days while the drug is being taken, with an additional count one week after it has been discontinued.

When laboratory work is unavailable because of inaccessible location or in time of war, the following points, as stated by Long,⁸ should be watched:

First, if there is any history of toxic reaction in any previous therapy with these drugs, it must be remembered that there will probably be a second, earlier and more severe reaction. In these cases a small test dose must be given and the reaction closely watched.

Second, the patient should be seen daily and observations made for the following toxic signs:

- 1 Body aching, headache or malaise (toxic)
- 2 Sclera observed for jaundice (hepatic involvement)
- 3 Mucous membrane examined for pallor (anemia)
- 4 Skin examined for rashes (more severe toxemia)
- 5 Temperature and chills (more severe toxemia)
- 6 Urine should be *measured* and observed for blood (in order to anticipate anuria and kidney congestion)

By observation of the above, all toxic symptoms may be anticipated.

excepting acute leukopenia, but no death has been reported during the first twelve days of treatment due to disturbances of the white blood cells

The introduction of sulfanilamide directly into the sinuses and ears is still in the experimental stage

Chemotherapy has unquestionably added greatly to the confidence of physicians in their ability to conquer acute otitis media, mastoiditis and fulminating sinusitis. We have always been apprehensive of meningitis as long as the ears and sinuses continued to discharge. In the twenty-five years prior to 1936, only 76 recoveries from streptococcic meningitis were reported in the literature, since 1936, more than 200 recoveries have been reported and mortality has dropped from 97 per cent to less than 35 per cent, and will drop still lower.⁹ This is a great comfort and a signal achievement. Yet one should be ever mindful of the fact that chemotherapy when used in ear and nose infections so obscures the clinical picture that there is an increased danger of the unheralded sudden onset of grave complications, such as meningitis and osteomyelitis, and that under the influence of these drugs all the symptoms of mastoiditis and sinusitis may disappear while the lesion is actually spreading.

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A CRITICAL EVALUATION OF THE RESULTS OF ROUTINE CONSERVATIVE TREATMENT OF SYPHILIS*

HAROLD THOMAS HYMAN

THE SCOPE OF THE SYPHILIS PROBLEM IN THE UNITED STATES

I N a recent survey,¹ routine blood tests gave serological evidences of syphilis in forty-four of every thousand American citizens. If these figures accurately depict the national situation, approximately 6,000,000 of our 130,000,000 citizens have been infected with lues. Of the 6,000,000 syphilitics, one half million are newly reported annually.¹

Cardiovascular syphilis¹ accounts for 40,000 deaths each year. The domiciliary care of patients with dementia paralytica costs \$31,000,000 annually.¹ An additional \$10,000,000 is spent per annum for pensions and the care of the syphilitic blind.¹ Before the advent of the National Campaign for the Control of Syphilis, more than 60,000 syphilitic babies¹ were born annually within our borders.

The prevention and treatment of syphilis are formidable problems with widespread individual, communal and national consequences.

THE INDIVIDUAL AND THE SYPHILIS PROBLEM

The venereal diseases have been widely publicized in the lay press and over the air waves. This dissemination of medical information has marked a signal accomplishment in public health education. It has also given rise to considerable "syphilophobia" and certain misconceptions concerning the disease and its management. The Wassermann-negative members of the community scrutinize suspiciously their compatriots as possible integers in the moiety that makes up the Wassermann-positive portion of our population. The Wassermann-positive citizens view the future with dread, believing (1) that they are an infectious menace to the community and (2) that untreated, they face cardiovascular disease, blindness or insanity. Treated, they are told without adequate qualification, that "syphilis is curable."

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REASONS FOR THE PRESENT SURVEY

At the present time we are engaged in a national emergency. Our citizenry is being mobilized for service in the armed forces and in industry. It is a time when a national program for the control of syphilis may be instituted with a great prospect of significant achievement.

Simultaneously, the medical profession has been given a new form of attack^{2, 3, 4} aimed at the treatment and possible eradication of syphilis. Massive dose chemotherapy by the intravenous drip method⁵ gives promise of a high incidence of curability with a low, but definite, treatment hazard. During the period of the five days of active treatment, the patient is institutionalized and removed from contact with the community.

Preliminary to a discussion of the national program for the control of syphilis, it has seemed desirable to survey critically the results of the routine treatment of syphilis by conservative methods. In the light of these data, the relative risks and possible benefits of the more radical treatment may be measured, at a later time.

THE ESTABLISHMENT OF A THERAPEUTIC INDEX UNDER
LABORATORY CONDITIONS

Under the ideal conditions that exist in the laboratory, it is relatively simple to establish the therapeutic index of any specific drug that might be used in the treatment of a given infection.

Healthy standard animals are inoculated, under constant and supervised conditions, with a single strain and a uniform dose of the pathogen. Specific therapy is withheld from a "control" group, so that the incidence of "spontaneous cure" may be estimated. The remainder of the infected animals, under otherwise constant conditions, receive varying doses of the specific chemotherapeutic agent.

Toxicity is determined by (1) the sacrifice, at varying intervals, of treated animals, (2) the observations of the non-fatal complications in the survivors, and (3) autopsy of those who have succumbed to the lethal effect of the drug ("treatment deaths").

The therapeutic efficacy of the drug is estimated by a comparison of the recovery rate in the treated and controlled group.

The therapeutic index is gauged by balancing treatment risk against therapeutic efficacy.

THE VARIABLES IN CLINICAL CHEMOTHERAPY

Clinical chemotherapy presents a much more intricate problem. It involves many variables relative to (1) the host, (2) the parasite, (3) the circumstances of the host-parasite interaction, (4) the therapeutic variables relative to time-dose factors, (5) the individual variations in the absorption, concentration or excretion of the drug, and (6) the social and economic costs and implications of therapy.

THE VARIABLES IN THE CHEMOTHERAPY OF SYPHILIS

More concretely, the discussion which follows deals with the factors that must, of necessity, be evaluated in the estimation of the accomplishments of chemotherapy of syphilis by current conservative methods. The variables include (1) those relative to the individual patient (age, sex, color), (2) those pertinent to the strain and dose of the specific spirochete, (3) those incidental to the host-parasite inter-relationship, specifically with regard to morbidity, mortality and the spontaneous course of untreated syphilis, (4) those referable to the stage of the disease when therapy is instituted, (5) those referable to the nature, preparation and dose of the therapeutic agent or agents that are employed, (6) those pertaining to the presentation of statistics.

I THE HOST

Congenital syphilis in infants is commonly fatal (Jeans and Cooke⁶).

Acquired syphilis in the prepubescent or elderly patient is prone to be most florid in its manifestations (Fournier⁷).

Women more frequently have asymptomatic infections than men.⁸ Pregnancy favors the production of asymptomatic infection.⁹

Race and color alter the course of syphilis. The negro is more apt to develop cardiovascular lues.¹⁰

Amongst the variables pertinent to the host, syphilis may vary with age, sex and color.

2 THE PARASITE

Little is known concerning variations in the virulence of strains of spirochetes. However, the quantity of the inoculum may determine the clinical manifestations. Asymptomatic infection¹¹ may be induced, in the rabbit, by decreasing the amount of inoculum to a point where demonstrable lesions do not occur.

3 THE HOST-PARASITE INTER-RELATIONSHIP

The host-parasite inter-relationship is concerned with the problems of virulence, resistance and immunity. The ledger that scores the results of the conflict may be concerned with (A) morbidity, (B) mortality, (C) the spontaneous cure of untreated syphilis.

(A) Morbidity of Early Syphilis

The morbidity and mortality of treated and untreated syphilis are difficult to estimate. Russell¹ has stated that 16.9 per cent of patients with untreated syphilis develop symptomatic neurosyphilis. Another 3.4 per cent develop cardiovascular syphilis. The morbidity for the disease from these two complications alone is thus slightly in excess of 20 per cent.

These figures may be compared with the data obtained by Bruusgaard¹² who attempted to learn the further course of 2181 untreated patients afflicted with primary or secondary syphilis. Bruusgaard traced 473 or 22 per cent of these patients. Of the 309 living individuals, only 35 per cent had clinical evidences of syphilis. Of 164 patients who died, for whatever reason, only 49 or 30 per cent died of syphilis.

(B) Mortality of Early Syphilis

Other than in congenital syphilis, immediate death from syphilis does not occur, at the present time.

The late mortality, in the Bruusgaard series, approximated 30 per cent of deaths caused directly by the ancient luetic infection.

(C) The Spontaneous "Cure" of Early Syphilis

It has been indicated above that but one-third of the syphilitics suffer from clinical lues. What is the fate of the remaining two-thirds? Is it possible for the host-parasite conflict to go on to a stalemate, the serology remaining positive and the patient clinically well? Is it possible for the host to triumph, the parasite to be vanquished, and the patient to undergo spontaneous cure with negativity of blood tests?

Sowder¹³ has recently earned the gratitude of all students of syphilis by his survey of the Bruusgaard material. These data, may with profit, be briefly reviewed.

Under the aegis of Boeck who believed that the then-available specifics (potassium iodide and mercury) interfered with the host-parasite

relationship, specific therapy was withheld from his patients with early syphilis during the twenty year period from 1891 to 1910. In 1929, Bruusgaard reported on his efforts to contact the original 2181 patients included in this untreated group.

Information was obtained of 473 persons (22 per cent). Three hundred and nine of the patients were living. One hundred and sixty-four had died. Amongst the 309 living, 110 (35 per cent) had evidences of clinical syphilis. Sixty-eight (22 per cent) were clinically well with positive blood findings. One hundred and thirty-two (43 per cent) were clinically well with negative blood tests. Thus, the total clinically well, including the serologically positive group, was 200 patients or 65 per cent.

The analysis of 164 deaths reveals that 49 (30 per cent) died of syphilis. The remaining 70 per cent died of pulmonary tuberculosis, cancer, tumor or other causes.

Thus, of the 473 patients, living and dead, approximately one-third suffered from or died of syphilis. The remaining two-thirds were either clinically well or succumbed from other causes.

Sowder ably discusses the factors of selection. The baffling problem is the fate of the lost 1708 patients (78 per cent). Sowder concludes, with seeming justice, that the direction of the selection has been to exaggerate the gravity of the disease rather than to minimize it. The smaller group of followed cases included all or nearly all of the original patients who developed neurosyphilis and cardiovascular syphilis, as well as those who died of the disease. The larger group of 78 per cent, who were not followed, included few with neurosyphilis, cardiovascular or visceral syphilis, and few who succumbed to the disease. It is reasonable to assume that the "lost" group contained a relatively larger number of those who were clinically and serologically well. The reported group was probably weighted with the graver manifestations.

Employing, as a yardstick, the experience of Bruusgaard, the efficacy of any specific therapeutic measure must be one which will produce favorable results in excess of the 66 per cent expected "cure" rate of the spontaneous course of the disease.

(D) *The Spontaneous Course of Late Syphilis*

Supplementing the Bruusgaard studies, the Cooperative Clinical Group¹⁴ has hypothecated the spontaneous course in untreated latent

syphilis According to these prognostications, 25 to 35 per cent of the patients will go on to spontaneous "cure" An additional 25 to 35 per cent will be clinically well but serologically positive The remaining 50 to 30 per cent will suffer from symptomatic syphilis including benign and late cardiovascular lues, neurosyphilis and visceral syphilis

Specific treatment must appreciably transcend these results, if the therapeutic effort is to be justified

4 VARIABLES RELATIVE TO TREATMENT

The evaluation of therapy in syphilis has already been shown to be modified by variables referable to the host and the host-parasite relationship To these, must be added the variables dependent upon treatment

The modern treatment of syphilis (excluding syphilis of the nervous system) is carried out with three of the heavy metals arsenic, mercury and bismuth Each of the heavy metals may be administered by several routes, employing several preparations For the most part, arsenical therapy is given intravenously, and the arsphenamines and arsen-oxide are the preparations of choice Bismuth is given orally or by intramuscular injection Mercury may be given by inunction, by mouth, by intramuscular or occasionally, by intravenous injection

The drugs may be given alone or in combination

Treatment schedules agree in these respects

- 1 The patient is given ambulatory treatment with divided doses
- 2 The course of therapy, to be effectual, must be carried out for no less than a year, more often for two years, with an average of eighteen months or more, even under the most favorable circumstances

Certain types of conventional routine treatment of syphilis may be recognized

- 1 *Irregular treatment*, as the name implies, indicates that the patient has received spasmodic injections at such times as he has appeared at the clinic
- 2 *Intermittent treatment* is accomplished by alternating a series of injections of arsenic and bismuth or mercury, followed by periods of rest
- 3 *Continuous treatment* provides for alternation of courses of arsphenamine and courses of bismuth or mercury Either of the latter overlaps the last arsenic injections of the previous series and the first arsenic injections of the succeeding series

- 4 The "*best available conventional method of treatment*," as practiced by Moore, provides for continuous treatment as above and continued treatment
- 5 *Continuous alternating or concurrent standard treatment* consists of at least thirty injections of an arsenical and at least forty injections of a heavy metal without any interruptions greater than one month (USP HS)

Thus, a classical schema, such as proposed by Cole¹⁵ for the treatment of early syphilis, calls for eleven injections of an arsenical in the first ten weeks, followed by six doses of bismuth at weekly intervals, another group of ten arsenicals, followed by eight bismuths, a third series of ten arsenicals followed by a third series of ten bismuths, a fourth series of ten arsenicals and ten bismuths

The total span of therapy thus occupies seventy-five weeks. The patient receives no treatment from the seventy-fifth to the one hundred and third week, and then returns for a complete check-up. The continuous treatment is then continued, if necessary ("best available conventional method")

In latent syphilis, the Moore plan¹⁶ (as carried out at the Vanderbilt University Hospital Syphilis Clinic) is initiated by three weekly doses of bismuth, followed by eight weekly doses of the arsenical, a second series of eight weekly doses of arsenic followed by twelve weekly doses of bismuth, a third series of eight arsenicals and then twelve bismuths. There then follows a rest period from the fifty-eighth to the sixty-ninth weeks. This is succeeded by twelve weekly doses of bismuth, a rest period from the eighty-second to the ninety-third weeks, and another series of twelve weekly bismuth injections which carries through to the one hundred and fifth week, or two years.

Thus, the treatment systems of syphilis vary widely from the haphazard, irregular type through the intermittent form up to the highly regimented continuous and continued methods, as practiced by the best syphilologists.

RESULTS OF VARIOUS TYPES OF THERAPY IN EARLY SYPHILIS

Omitting from consideration, for the time being, all factors other than the type of treatment, the efficacy of each of these methods has been discussed most recently by Padget.¹⁷ Reporting from Johns Hopkins Hospital, Padget selected, from approximately 6000 individuals with

early syphilis, a group of 551 patients who "had been completely re-examined five years or more after the termination of the original treatment for early syphilis" The outcome of the remaining 5449 is not discussed

(A) *Spontaneous Course*

In the Padget series of 551 patients, 17 received no treatment and, of these, 35 per cent were clinically and serologically clear One additional patient (5.9 per cent) was clinically well but serologically positive Thus, of the untreated group, over 40 per cent had no clinical manifestations of the disease

(B) *Intermittent or Irregular Treatment*

Two hundred and eighty-eight patients received intermittent or irregular treatment Approximately 50 per cent of these were cured Another 20 per cent were clinically well but serologically positive The total of satisfactory cases approximated 70 per cent

The outcome of therapy in this type of management led Padget to say "In view of this essential uselessness of grossly irregular treatment in preventing the development of crippling late lesions of syphilis in the individual and its effect in the prolongation of the potential period of infectious relapse, is there any justification for the expenditure of the relatively large amount of effort which may be required to get an occasional treatment into an essentially uncooperative patient? Is it perhaps not only permissible, but actually desirable, to allow such patients to go their way unmolested once they have demonstrated their unwillingness to cooperate? It is interesting that for entirely different reasons this point of view which prevails in Great Britain has recently been warmly supported by Harrison," and again, "The palpable inferiority of irregular and intermittent treatment strongly suggests that, if continuous treatment cannot be given, no treatment is the desideratum"

(C) *Continuous Treatment*

Continuous treatment was accomplished by 246 of Padget's group of 551 patients Of these, it is reported that 83.4 per cent were cured An additional 8.5 were clinically well, though serologically positive Thus, approximately 92 per cent had a satisfactory response and but 8 per cent were suffering from infection

(D) *Continuous and Continued Treatment*

Of the last group of 246 patients receiving treatment, 155 patients not only received continuous treatment but also continued their treatment. It is to this group that Moore refers when he speaks of the "best available conventional methods of treatment." In this small group (which constitutes 2.5 per cent of those who originally entered the clinic) 90 per cent are cured and another 5 per cent are clinically well but serologically positive, making a total of 95 per cent of satisfactory results.

In the Padgett series, of selected cases of early syphilis, dependent wholly upon the system of therapy, the results vary between the "palpable inferiority" of the irregular and intermittent treatment, and the "highly satisfactory results" of the "best available conventional methods of treatment." The latter group constituted 28 per cent of the selected series, which made up 2.5 per cent of the original 6000 patients. It is possible that some of the unreported cases received optimum therapy, but these records are not included in the present report.

CASES HOLDING WITH CONVENTIONAL TREATMENT

The first problem in the mass attack on syphilis is the establishment of an optimum system of treatment. The next challenge is the practical execution of that therapy.

Minimal adequate treatment has been defined by the Public Health Service as the accomplishment of the intravenous injection of 20 doses of an arsenical and 20 doses of bismuth within the first year of treatment.

Russell¹ has recently attempted to determine the percentage of patients with early syphilis who succeed in receiving minimal adequate treatment. Reporting from the United States Public Health Service, Russell studied 6,807 patients. Eighty-four per cent received less than twenty treatments, 11 per cent received less than thirty, and but 1.4 per cent received forty or more treatments. Of a second group of 590 patients, 328 received "inadequate" treatment, and 191 patients received "less than standard treatment." Thus, a total of 519 or 90 per cent received inadequate or less than standard treatment, and but 10 per cent received adequate treatment.

In the United States as a whole, Russell estimates that 95 per cent of the patients with early syphilis received inadequate treatment by conventional methods.

5 CASE LOSS AND STATISTICS

In face of a formidable case loss in conventional therapy, how is the syphilologist to evaluate therapy? If treatment is started in 100 patients, the majority may be expected to disappear from observation and become case losses. Are these patients to be reported as failures? If statistics are presented in this way, the maximum number of "cures" even if it includes all of the faithful, cannot approach the expectancy of spontaneous "cure."

On the other hand, if the statistics are based upon the patients that are followed, the reported results ignore the "lost" patients and present a false picture of the efficacy of treatment.

Morgan inquires, "What of those who receive inadequate treatment?" and responds, "It has been clearly demonstrated that inadequate treatment often reacts unfavorably on the course of the disease. The data supplied by the Cooperative Clinical Group, indicates that 13 per cent of the patients inadequately treated, redevelop acute infectious lesions, whereas only 2.7 per cent who receive 20 or more injections experience such recurrence."

The evaluation of specific therapeutic measures must represent the results obtainable in a consecutive series of patients. Presentations should state the total number of patients who initiated therapy and the total number of patients who completed therapy.

Our national problem, in the treatment of syphilis, concerns itself with the management of every syphilitic, not with the smaller group who can and will undergo the sacrifices and requirements of routine conventional therapy.

6 VARIABLES REFERABLE TO THE STAGE OF THE DISEASE AT THE INITIATION OF TREATMENT

The final variables to be discussed relate to the stage of the disease at the time of the initiation of therapy.

(A) *In Early Syphilis*

All syphilologists are in agreement that optimum results are to be anticipated in the treatment of early syphilis (primary sero-negative, primary sero-positive, and secondary lues). Less favorable chemotherapeutic achievement is anticipated in early latent, visceral or late latent

syphilis The consideration of neurosyphilis is omitted from the present discussion

Concentrating upon the results in early syphilis, there are two methods of presenting the results of specific therapy Thus, Moore states¹⁸ that the "chance for cure in the various stages of early syphilis employing the best available present day treatment" is 100 per cent in sero-negative primary syphilis, 95 per cent in sero-positive primary syphilis, and 90 to 95 per cent in early secondary syphilis

This "chance for cure" is to be compared with the actual figure as presented from the same clinic This report¹⁸ indicates that in 140 cases of sero-negative primary syphilis, satisfactory clinical outcome occurred in 71.4 per cent, in 274, with sero-positive syphilis, a satisfactory outcome occurred in 53.3 per cent, in 910, with early secondary syphilis, satisfactory results were obtained in 49.8 per cent

Again, in the Padgett series of sero-negative primary syphilis, the percentage of cure was 82, in sero-positive primary syphilis, the percentage was 55, in secondary syphilis, 68 per cent, whilst, in early latent syphilis, there were but 58 per cent cured

Treating similar material with mapharsen, Chargin, Leifer and Rosenthal,¹⁹ in 188 cases, report 84 per cent satisfactory results

How can these various figures be conciliated? Reference to the previous section clarifies the Moore figures concerning the "chance for cure" By this is clearly meant, the "chance for cure" in those patients who completed continuous and continued treatment ("the best available present day treatment") This type of therapy was achieved by 155 of the 551 patients reported by Padgett, the whole group having been selected from a total of 6000 individuals who initiated therapy More succinctly stated, the figures for "chance for cure" are based on the experiences of 2.5 per cent of the whole group The remaining figures, stated in terms of the number of patients actively treated, are based not upon those who initiated therapy, but those who completed therapy and were adequately followed In no instance, are the calculations based upon the total number of patients who suffered from primary or secondary infectious syphilis and who sought therapy by the routine, conservative method

THE MORBIDITY OF ADEQUATELY TREATED EARLY SYPHILIS

Against the achievements of specific therapy must be weighed the

morbidity and mortality of the disease, the morbidity and mortality resulting from therapy

In his small group of followed cases Padget, whose splendid report may well serve as a model, reports 3.8 per cent of his patients with benign late syphilis, 4.5 per cent with cardiovascular syphilis, 12.3 per cent with neurosyphilis, 1.3 per cent with multiple late manifestations, and a single patient who was treatment resistant

Thus, the morbidity from the disease in these well treated and well followed patients totalled 19.4 per cent

The mortality in the treated series showed that 1.8 per cent of the adequately treated patients died of syphilis (three from aortic regurgitation and seven from general paresis)

It is unfortunate that we are not in possession of the statistics concerning the morbidity and mortality in the unreported patients who began therapy. One may only speculate as to the circumstances. Souder has, with justice, intimated that the "lost" group in the Bruusgaard series probably showed less evidences of the ravages of syphilis than the group that was followed, i.e., the followed group was weighted with the more serious complications. It would seem reasonable to assume that the opposite conclusion held in the unreported group in the Padget series. These patients received inadequate treatment and their roster must be weighted with the graver manifestations of the disease.

To the morbidity and mortality of the disease itself must be added the morbidity and mortality incident to treatment. In the Padget series forty-three patients sustained serious reaction to treatment (8 per cent). Nineteen of the group had arsphenamine dermatitis, eighteen had post-arsphenamine jaundice, two had both complications, one patient had a blood dyscrasia. The others were scattering. There were no reported treatment deaths.

What of the treatment morbidity and mortality in the lapsed group? Is it possible that some of the patients who failed to return suffered reactions that discouraged them from continuing therapy? Is it possible that treatment deaths (which commonly seem to occur in routine treatment once in three hundred to once in four hundred patients) may have occurred in the lapsed series and that such patients are classified as case losses? The question is posed because of our experience that the serious and fatal arsenical complications often make their way to another institution rather than to the ambulatory treatment clinic where therapy was administered.

TABLE I

ESTIMATE OF THE PROBABLE OUTCOME OF LATENT SYPHILIS
(Moore, Bruusgaard, and C C G)

	Cure	Latent Infection	Late Syphilis (Skin Mucosal Osseous)	C V Syphilis	Neuro Syphilis	Other Visceral Syphilis
	per cent	per cent	per cent	per cent	per cent	per cent
Untreated	25-35	25-35	10-15	10-15	1-2 0	0 5-1
Adequately treated early syphilis	70-80	20-25	2-5	2-5	1-2	0 5-1
Adequately treated late syphilis	60-70	25-35*	1 6	1 6	1 6	

* Wassermann fast

(B) LATE SYPHILIS

The evaluation of the efficacy of therapy becomes increasingly more complicated in late syphilis. Morgan¹⁶ has presented a table in which there is estimated the probable outcome of latent syphilis, as based upon the experiences of Moore, Bruusgaard and the Cooperative Clinical Group. This chart is reproduced herewith (Table I).

The critical reader may ponder upon the relationship that exists between these estimated results, and the actual figures in terms of patients treated. How can these prognostications be conciliated with the citation by Morgan of Moore's statement that "about 35 per cent of all patients with late latent syphilis are persistently Wassermann-positive under any form of treatment." If this be accepted, treatment-results in latent syphilis must more nearly approach the Bruusgaard figures for spontaneous cure than the "chance for cure of early syphilis, employing the best available present day treatment."

SUMMARY

1. Critical evaluation of the results of the routine conservative treatment of syphilis requires a consideration of the modifications that arise due to the interpolation of several variables.
2. The course of syphilis may vary with the age, sex and race of the host.

- 3 The course of the disease may vary, dependent upon the quantity of the inoculum
- 4 Studies of the "spontaneous" course of early syphilis indicate that one patient in three will suffer clinical manifestations of the disease
- 5 The "spontaneous" course of early syphilis tends to "cure" in approximately 43 per cent of all patients, and an additional 22 per cent will remain clinically well with positive serology. Thus, two patients in three, afflicted with early syphilis, may be expected to live their lives and eventually succumb without clinical manifestation of the infection
- 6 The incidence of expected "spontaneous cure" of late syphilis approximates but does not quite equal the anticipated incidence in early syphilis
- 7 The results of therapy in syphilis vary with the treatment schedules. All schedules agree in that the patient is given ambulatory treatment, with divided doses, over the course of a long period of time, averaging perhaps in excess of eighteen months, even under the most favorable circumstances
- 8 The protracted nature of the therapy results in a "case loss" approximating 80 per cent under optimal conditions, and exceeding 90 per cent in a nation-wide survey
- 9 Those patients who make up the larger group of "case loss," have necessarily received inadequate treatment. The best authorities agree that inadequate treatment often reacts unfavorably on the course of the disease. The "case losses" make up the reservoir of infectious syphilis
- 10 Under optimal conditions in the well-organized clinic, the minority of those who have initiated therapy receive minimal adequate treatment. Under nation-wide conditions, the number who receive 20-20, (20 injections of arsenic intravenously and 20 injections of the heavy metals intramuscularly over the span of a single year) is perhaps in the vicinity of 5 per cent
- 11 Those who complete adequate minimal treatment receive courses by several methods, i.e., the irregular, the intermittent, the continuous or the continuous and continued, the last named constituting the "best available conventional method of treatment"
- 12 Syphilologists state of irregular treatment, that it is "essentially useless"

- 13 Of irregular and intermittent treatment, it is stated that their "palpable inferiority strongly suggests that if continuous treatment cannot be given, no treatment is the desideratum"
- 14 As a positive contribution to the specific chemotherapy of syphilis, there remains only the continuous form of treatment
- 15 Only a small percentage of patients initiate therapy and remain under active treatment until the satisfactory continuous course of therapy has been completed
- 16 So far as can be mathematically proven, specific chemotherapy exceeds the result of the spontaneous course of the disease only in the treatment of early syphilis by the continuous method. The treatment-results reported in latent and visceral syphilis seem not greatly different from the "spontaneous cures" experienced by the Bruusgaard patients from whom all specific therapy was withheld
- 17 The great triumph of specific chemotherapy in syphilis seems sharply limited to those patients with early syphilis (constituting perhaps 16 per cent of Wassermann-positive individuals) who have persisted through continuous and continued forms of therapy (5 per cent of those who initiate therapy)
- 18 The more glowing reports of specific chemotherapy in syphilis are based upon "expectation of cure" rather than upon actual statistics. The available statistics that are published do not consider the total number of patients that initiated therapy. They ignore the majority of infected individuals who have lapsed from therapy
- 19 The statement, "syphilis is curable," requires many qualifications

CONCLUSIONS

The present day management of syphilis by the conventional methods of treatment is pitifully inadequate for our national program for the prevention and treatment of this dread disease.

The attack against syphilis must realistically recognize these fundamental tenets:

- 1 Treatment must be focused upon early syphilis
- 2 The completion of therapy for early syphilis must be mandatory, not optional
- 3 During the infectious stage, the patient must be institutionalized
- 4 Practically, to accomplish these aims, the intensity of therapy must be increased, so that the duration of treatment is sharply decreased

- 5 The results of specific therapy must transcend the expectancy of spontaneous cure
- 6 The computation of results must be based on the total number of patients initiating treatment

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DEATHS OF FELLOWS

BANTING, SIR FREDERICK GRANT 205 Rosedale Heights Drive, Toronto, Ont., Canada, born in Alliston, Ont., November 14, 1891, killed in an airplane accident near Musgrave Harbor, Newfoundland, February 21, 1941, received from the University of Toronto, Faculty of Medicine, the degree M.B. in 1916 and M.D. in 1922, elected an Honorary Fellow of the Academy March 2, 1933

Dr Banting was resident surgeon to the Hospital for Sick Children in Toronto, Ont. 1919-20 and part-time assistant in physiology at the Western University Faculty of Medicine, London, Ont. 1920-21. In May 1921, he commenced research on the internal secretion of the pancreas at the University of Toronto, Ont. At that institution, he was also lecturer on pharmacology, 1921-22, and senior demonstrator in medicine, 1922-23. Since 1923 he was professor of medical research in the Banting and Best Department of Medical Research, a chair which was established by the University of Toronto in recognition of his work on insulin. He was honorary consulting physician to the Toronto General and Toronto Western Hospitals.

In 1922 he was awarded the Starr Gold Medal and the George Armstrong Peters Prize and in 1923 the Charles Mickle Fellowship and the Reeve Prize, all of the University of Toronto. In 1923 he shared the Nobel Prize with Dr J. J. R. MacLeod. In 1924 he was awarded the John Scott Medal by the city of Philadelphia and received a life annuity of \$7,500 from the parliament of Canada. In 1924 he was awarded the Rosenberger Gold Medal by the University of Chicago. In 1927 the Cameron Prize by the University of Edinburgh, in 1931 the Flavelle Medal by the Royal Society of Canada. In 1934 the Apothecaries Medal of London. In 1936 the F. N. G. Starr Gold Medal by the Canadian Medical Association.

Dr Banting was knighted a Commander of the Civil Division of the Order of the British Empire in 1934. He was a licentiate of the Royal College of Physicians, member of the Royal College of Surgeons, fellow of the American College of Physicians, fellow of the Royal College of Surgeons of England, fellow of the Royal College of Surgeons of London, fellow of the Royal College of Surgeons of Canada, fellow of the Royal Society and fellow of the Royal College of Physicians. He was an honorary fellow of the Academy of Medicine of Toronto, honorary member of the Norwegian Medical Society in Oslo, foreign correspondent, Académie royale de médecine de Belgique, La Società medico-chirurgica di Bologna, corresponding member of the Royal Medical Society of Budapest, member of the Canadian Medical Association, American Society for Pharmacology and Experimental Therapeutics, British Physiological Society, Association of American Physicians, Canadian Chemical Association, American Association for Cancer Research and the Imperial German Academy of Natural Sciences.

For three years during the World War, Dr Banting served with the Canadian Army Medical Corps, and he was again serving as a major in the medical corps of the Canadian Army at the time of his death. In 1918 he was awarded the Military Cross. He held honorary degrees from the University of Toronto, Queen's University, University of Western Ontario, Yale University and the University of the State of New York.

BURRITT, CLAUDE ADELBERT 1 East 105 Street, New York City, born at North Greece, Monroe County, New York, July 13, 1878, died in New York City, March 3, 1941, graduated in medicine from the Cleveland Homeopathic Medical College in 1905, elected a Fellow of the Academy November 4, 1937.

Dr Burritt was director of the pathogenic laboratory and instructor in toxicology at the University of Michigan College of Homeopathic Medicine, Ann Arbor, from 1905 to 1908. From 1908 to 1913, assistant professor of genito-urinary surgery, der-

matology and electrotherapeutics, and from 1913 to 1914, professor of surgery and genitourinary surgery. At the Ohio State University College of Homeopathic Medicine, Columbus, Dr Burrett was professor of surgery and acting dean from 1914 to 1915, and dean and professor of surgery from 1915 to 1922. At the New York Medical College, Flower and Fifth Avenue Hospitals, formerly known as the New York Homeopathic Medical College and Flower Hospital, he was dean, professor of surgery and director from 1925 to 1939, and its president since 1939.

Dr Burrett was a Fellow and a former member of the Board of Governors of the American College of Surgeons, a member of the Medical Council of the State Board of Regents, a trustee of Syracuse University, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

During the World War, Dr Burrett was surgeon to the student army training corps at Ohio State University and a member of the medical division of the Ohio Defense Board.

CRAWL, WALTER CONCEMERE 1001 Park Avenue, New York City, born in Hamilton, New York, April 12, 1878, died in New York City February 18, 1941, received from Colgate University the degree A.B. 1900, and D.Sc. 1923, graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1904, elected a Fellow of the Academy December 3, 1908.

Dr Cramp had practiced surgery in New York City since 1904. He was assistant professor of surgery at Bellevue Medical School for six years and at one time was visiting surgeon to the Willard Parker, St. Francis, and Bellevue Hospitals and the Hospital for Joint Diseases. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a Trustee of Colgate University, and a member of the State and County Medical Societies.

MACPHEE, JOHN JOSEPH 146 East 49 Street, New York City, born at St. Margaret, Prince Edward Island, Canada, July 8,

1860, died in New York City, February 18, 1941, graduated in medicine from the University of Vermont in 1890, elected a Fellow of the Academy December 7, 1905.

Dr MacPhee was emeritus professor of neurology at the New York Post Graduate Medical School, Columbia University, attending neurologist to the St. Francis Hospital and consulting neurologist to the Misericordia and Post-Graduate Hospitals, the Bronx Eye and Ear Infirmary, the Harlem Eye and Ear Infirmary, and St. John's Hospital at Long Island City. He was a Fellow of the American Medical Association, a member of the Association for Research in Nervous and Mental Disease, and a member of the State and County Medical Societies.

WENCKEBACH, KAREL FREDERIK Vienna, Austria, born at The Hague, Holland, March 12, 1864, died in Vienna, November 11, 1940, elected an Honorary Fellow of the Academy March 2, 1933.

After receiving his medical degree from the University of Utrecht, Dr Wenckebach was appointed in 1888 as assistant in the Institute of Zoology, and afterwards in the Department of Pathology and Normal Anatomy. In 1901 he was elected professor of internal medicine at Groningen, and from 1911 to 1914 he held the same post at the University of Strasbourg. He was then called to the chair of medicine at the University of Vienna, as professor of medical pathology and therapy, and was made emeritus professor of medicine in 1929. Throughout those years Wenckebach identified himself with progress in the study, pathological and clinical, of diseases of the heart and circulatory system, publishing many important contributions to cardiological knowledge between 1901 and 1932. For some years he edited, jointly with Drs Falta and Jagic the *Wiener Archiv für innere Medizin*.

Dr Wenckebach was an Honorary Fellow of the Royal College of Physicians and of the Royal Society of Medicine, and a Foreign Corresponding Member of the British Medical Association. He was noted as the founder of the science of electrocardiography and achieved fame as one of the first students in the study of the arrhythmias of the heart.

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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BULLETIN OF
THE NEW YORK ACADEMY
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JULY 1941

EPIDEMIC ENCEPHALITIS *

RALPH S MUCKENFUSS

Director of Bureau of Laboratories New York City Department of Health

THE clinical picture of encephalitis was first brought to attention in 1917 when von Economo¹ described an outbreak of encephalitis which he called "lethargic encephalitis." During the following few years this disease was recognized as widespread over the world, and it shortly became apparent that the term "lethargic" was a misnomer. The accepted title was accordingly changed to "epidemic encephalitis."

For a time this term appeared satisfactory, but in 1924, 1927, and in several succeeding years a different form of encephalitis appeared in Japan. This type occurred characteristically in the late summer instead of predominating in the winter months, and had other features that classed it as a disease different from that described by von Economo. Kaneko and Aoki² designated this disease "type B" to distinguish it from the disease of von Economo, which was called "type A."

In the late summer of 1933 an epidemic of encephalitis similar in many respects to Japanese type B occurred in the city of St. Louis. This has been shown by investigations in the last few years to be of a different etiology from that of the Japanese disease.

* Read October 25, 1940 in The Graduate Fortnight of The New York Academy of Medicine.

An epidemic of encephalitis caused by the virus of equine encephalomyelitis of the eastern type occurred in Massachusetts in the summer of 1938, and in the same year human infections with the virus of the western type were reported

Recently, encephalitis occurring in the spring and early summer in Russia and Siberia, and caused by a virus immunologically different from the viruses of St. Louis or Japanese encephalitis, has been described

Thus it is evident that the term "epidemic encephalitis" must be broadened and that its use alone is no longer sufficient as a diagnosis. Retaining this general designation, the different forms of encephalitis, including von Economo's disease, Japanese encephalitis, St. Louis encephalitis, equine encephalomyelitis of the eastern type, equine encephalomyelitis of the western type and the recently described Russian encephalitis, must be differentiated. Australian X disease is a form of encephalomyelitis apparently occurring in epidemic form, but information concerning it is so limited that it will not be included in the present discussion.

Admittedly, there may still be cases of encephalitis of diverse and, as yet, unrecognized etiology. Future discoveries may necessitate still further differentiation.

ETIOLOGY

All of the diseases included under the generalization "epidemic encephalitis" are either caused, or presumed to be caused, by filterable viruses.

The disease described by von Economo was the first of the group to be recognized, and has been subjected to the most intensive investigations without success in establishing its etiology. Streptococci have been repeatedly suspected, but none of these claims has been sustained by further research. Several viruses have also been suspected, and the evidence is strongest for the herpes virus,³ which is presumed to acquire neurotropic properties making it capable of causing encephalitis. Attractive as this hypothesis is, there are serious objections to it.

Herpes virus is rather widespread among human beings, and is usually isolated with little difficulty. Many strains can readily be shown to possess neurotropic properties for animals. If herpes virus is the cause of von Economo's disease, it is a little difficult to explain why its isolation from human cases of the disease has so rarely been accomplished.

It is worthwhile noting that this virus has been isolated from the central nervous system of persons suffering from other diseases of known etiology and in whom epidemic encephalitis had not been suspected. Unfortunately, the specific diagnosis of this disease is necessarily attended by some uncertainty, but the clinical histories of cases from which herpes virus has been isolated justify one in questioning whether all of them were actually cases of epidemic encephalitis. It has also been shown⁴ that the occurrence of neutralizing antibodies against herpes virus in the blood of those suffering from the disease of von Economo is not significantly different from their presence in the general population.

These reports make it clear that herpes virus cannot be accepted as the established cause of the encephalitis of von Economo, and in my opinion the burden of evidence is against this virus having any part in its etiology. The cause of this disease must still be considered unknown.

St. Louis encephalitis is caused by a virus found in the central nervous system of fatal cases, and capable of causing a fatal infection in mice⁵ and a non-fatal infection in *Macacus rhesus* monkeys⁶ on intracerebral injection and in mice by intranasal instillation.⁷ Attempts to infect other animals have usually failed, although the virus can persist for a short time in the brains of guinea pigs and rats,⁸ and has been reported to have been passed serially in guinea pig brains⁹ and in mouse testicles.¹⁰ Histologically, the lesions produced in mice and in monkeys are analogous to those observed in humans. As described by McCordock,¹¹ "the essential pathologic process is an acute non-purulent inflammation of the central nervous system characterized by intense vascular congestion with petechial hemorrhages, cellular infiltration of both nervous tissue and meninges with various types of mononuclear cells, and evidences of toxic degeneration in the nerve cells." The virus of St. Louis encephalitis is neutralized by serum from persons who have recovered from the disease^{5, 12} and is immunologically distinct from other viruses^{5, 12, 13}

Japanese type B encephalitis resembles St. Louis encephalitis and is caused by a virus infectious for mice^{14, 15, 16} and monkeys^{14, 16}. The infection in these animals is more severe than that caused by the St. Louis encephalitis virus, and the pathological findings are similar, though varying in intensity. The Japanese encephalitis virus is neutralized by convalescent serum^{16, 17} and is immunologically different from the St. Louis

encephalitis virus^{17, 13} and other viruses¹⁵ However, there is some evidence that the Japanese virus may be somewhat related to the St Louis virus Kuttner and T'ung¹⁸ described two cases of encephalitis contracted by Europeans in China The serum of one of these protected against both the Japanese and St Louis encephalitis viruses and the serum of the other protected against the Japanese virus, but was not tested against the St Louis virus Webster¹³ later tested these sera and found they both protected against the Japanese as well as the St Louis virus Several Japanese investigators^{17, 19} have found that serum of rabbits immunized against the Japanese virus neutralized not only Japanese virus but also the St Louis virus

Equine encephalomyelitis occurs in two forms, the eastern type occurring east of the Appalachian mountains, and the western type occurring west of this mountain range The two types are immunologically different²⁰ A number of animals and birds are susceptible, and some of these have been found naturally infected These facts may be of considerable epidemiological importance and will be discussed in greater detail later

Russian encephalitis has recently been described^{21, 22, 23} as being caused by a virus to which mice and monkeys are susceptible This virus appears to be immunologically related to the virus of Japanese type B encephalitis, although the two are distinguishable by cross neutralization tests

EPIDEMIOLOGY

von Economo Encephalitis Numerous epidemics of von Economo's disease occurred throughout the world from 1920 to 1926, and since that time the incidence has been gradually diminishing It is reasonable at this time to consider it endemic rather than epidemic During the epidemic periods the incidence was highest during the winter months, during recent years this tendency to seasonal distribution has been less marked

With knowledge lacking concerning the etiology, there can be little certainty concerning the mode of transmission or factors directly affecting the spread of this disease The situation may best be summarized by quoting MacNalty²⁴ the "epidemiological concept of encephalitis is therefore similar to that of various epidemic diseases of the central nervous system, thus, while associated groups of cases or definite epidemics

sometimes come to light, the ordinary train of evidence is that only here and there does the widespread infecting agent find an individual who reacts with unmistakable illness manifested by a characteristic syndrome. Alternatively, the agent may infect the individual with such a massive dose, or in such a special manner that the characteristic disease is produced. In other words, for every definite and characteristic case of encephalitis lethargica there is a large and indeterminate number of people who receive and carry the infection without themselves suffering noticeably or at all."

St Louis Encephalitis Though it was first recognized as a new etiologic entity during the outbreak in St. Louis, the disease resembled an outbreak of encephalitis in Paris, Illinois in 1932. The form of encephalitis in St. Louis may also have been present in New York City in 1933. It was definitely present in Kansas City in 1933, and a virus identical with that isolated in St. Louis was recovered there.⁵ Sera from five convalescents in Paris, Illinois, in 1932, from two convalescents in New York City in 1933, and from four convalescents in Kansas City in 1933, were shown by Webster and Fite¹² to neutralize the virus of St. Louis encephalitis.

In the late summer and early fall of 1937 another outbreak of encephalitis similar to the one in 1933 occurred in St. Louis. This time a virus identical with that isolated in 1933 was recovered.²⁵ This was neutralized by serum of convalescents in 1933, and the 1933 virus was neutralized by serum of patients recovering from the disease in 1937.

Epidemics of St. Louis encephalitis have occurred characteristically in the late summer and early autumn. The fatality has averaged between 20 and 30 per cent and both the incidence and fatality have been higher in older age groups.

The etiological virus has been demonstrated only in the central nervous system of fatal cases. Failure to detect it in nasal washings or blood⁶ may be due to its complete absence, to its presence for only a short time, or to the inadequacy of technical methods employed. The manner of spread of St. Louis encephalitis is consistent with that for a disease transmitted by droplet infection and by carriers. That mice can be infected by dropping the virus in the nose supports this possibility. Although the virus has never been recovered from nasal washings, there is indirect evidence that it may be present. Sulkin, Harford and Bronfenbrenner²⁶ dropped nasal washings from cases of St. Louis encephalitis

into the noses of mice and, although none of them developed encephalitis, active immunity in a high percentage of the mice was evident on subsequent intracerebral inoculation of the virus

Whether a similar process of subclinical infection resulting in immunity occurs in man has not been definitely determined. But many investigators²⁷⁻²⁸ have reported the presence of neutralizing antibodies in presumably normal individuals—those who have no history of exposure to the virus. That such antibodies actually protect the individual against clinical infection is not known.

Biting insects were suspected as possible vectors, although the failure to demonstrate the virus in the blood stream makes it difficult to see how they could become infected. Experiments¹¹ designed to show transmission in this manner have uniformly failed, although Webster, Clow and Bauer²⁰ proved that *Anopheles quadrimaculatus* mosquitoes could become infected and would remain so throughout their entire lives. Mice rarely develop encephalitis if inoculated in any manner other than intracerebrally or intranasally. If mosquitoes are an important factor in the spread of St. Louis encephalitis, it is necessary to assume that infection through the skin by relatively small doses can be accomplished more readily in man than in experimental animals.

The situation concerning the transmission of St. Louis encephalitis was summarized by Leake¹¹ as follows: "In view of the trend of the insect experiments, the diffuse fashion in which poliomyelitis, except in the most intense epidemics, spreads through a community without apparent contact between cases, and in view of the radial spread of this epidemic of encephalitis by communities, but not by individual cases, it appears likely that human contact, chiefly through unrecognized carriers, is the method of infection here, but that susceptibility, in which age is an important factor, determines who will contract the disease in an infected community."

Contrary to Leake and his co-workers who could find no concentration of cases of encephalitis in any one district during the 1933 epidemic of encephalitis, Casey and Broun³⁰ reported that in 1933 and 1937 the cases of encephalitis in St. Louis were concentrated in the vicinity of small streams in areas characterized by the presence of weeds, refuse dumps, open sewage, and ponds. These are conditions that could favor the breeding and survival of mosquitoes.

Japanese Type B Encephalitis Epidemiologically, Japanese type B

encephalitis is similar to St Louis encephalitis, except that the fatality is higher, being over 50 per cent. The virus causes a more severe infection which is fatal in monkeys^{14, 16, 17} and it is also capable of infecting young sheep.¹³ It is uniformly present in the blood stream of mice in the early stages of infection, as demonstrated by Webster.¹³ Furthermore, intra-peritoneal or subcutaneous injection of the virus more frequently leads to infection in mice¹⁷ than does similar inoculation of mice with St Louis encephalitis virus. There are several reports^{14, 15} of isolation of the virus from the spinal fluid of patients, this has not been reported in St Louis encephalitis.

Mitamura and his co-workers³¹ are of the opinion that mosquitoes play a part in the spread of the disease. In 1933 they concluded that the outbreaks of Japanese summer encephalitis could be explained only on the assumption that the disease was transmitted by mosquitoes. In 1937, using three species of mosquitoes, it was found that virus ingested by mosquitoes decreased in amount for a period and then increased until it reached practically the same concentration as that originally present. This took place in 10 days with *Culex pipiens var pallens* and in from 15 to 20 days with *Aedes togoi*. Mosquitoes that had fed on human patients were also shown to be infective for mice.

Inada³² is of the opinion that Mitamura's results show clearly that mosquitoes are the true reservoirs of the virus and that they may transmit the disease to laboratory animals by biting. However, the objection is raised that the number of cases in the towns affected is not in proportion to the distribution of the mosquitoes.

Equine Encephalomyelitis There are at least five immunologically different forms of encephalomyelitis affecting horses.³³ Only the two forms occurring in the United States, the eastern and the western types, however, have been proved to infect man, and this discussion is accordingly limited to these two. Although there are differences, the similarities from an epidemiological standpoint are so great that both may be considered jointly.

The virus of equine encephalomyelitis is capable of infecting a number of animals³⁴ and birds.^{34, 35, 36, 37} For a short time during the early stages of the disease the virus is present in the circulating blood.³⁸ Experimentally, transmission is possible by mosquitoes^{33, 39} and by ticks.⁴⁰

In 1930, Meyer, Haring and Howitt⁴¹ demonstrated that an epidemic of encephalitis in horses in the San Joaquin valley was caused by a filter-

able virus, and that monkeys, rabbits, guinea pigs, rats and mice were susceptible, and that the guinea pig was the experimental animal of choice. Subsequently, in 1933, Ten Broeck and Merrill²⁰ isolated the eastern type of virus. In 1932 Meyer⁴² suggested that the unusual form of encephalitis contracted by three men working with infected horses might be due to the same virus. In 1938 an epidemic of encephalitis occurred in Massachusetts, and Fothergill and his associates⁴³ and Webster and Wright⁴⁴ isolated the virus of the eastern type. In the same year Howitt⁴⁵ isolated the virus of the western type from a fatal infection in California. A proven case of human infection also occurred in Minnesota.⁴⁶

In considering the epidemiology of equine encephalomyelitis, it should be remembered that it was first recognized in horses, and that many epidemics have occurred in this species, while in man sporadic cases have been recognized and only one small epidemic, that occurring in Massachusetts in 1938. The disease must therefore be primarily a disease of lower animals, capable of infecting man.

It is most natural to think of equine encephalomyelitis as a disease of horses, which suggests the horse as the reservoir of the disease. This is probably not the case. As pointed out by Ten Broeck, Hurst and Traub³⁸ the burden of evidence is against transmission of the disease by contact and in favor of some insect vector because of its prevalence in the late summer and fall, particularly in the salt marshes. However, the presence of the virus in the blood of horses for a relatively short time and the simultaneous occurrence of epidemics in widely separated areas are evidence against the horse as the reservoir. Based on this information, these authors, in 1935, suggested that birds should be considered as possible hosts, although at the time there was no direct evidence for this hypothesis.

In 1938, Tyzzer, Sellards and Bennett³⁶ recovered virus of the eastern type from an epidemic in ring-necked pheasants, and this observation was repeated by Van Roekel and Clarke.³⁷ Fothergill and Dingle³⁵ isolated virus from a pigeon. Moreover, a large number of birds and domestic fowls^{34, 47} have proven susceptible to laboratory infection. Ten Broeck⁴⁷ in 1939, showed that the virus is present in the blood of some fowls in higher concentration and for a longer time than in the horse.

Mosquitoes have received the most attention in searching for a vector, and eight species have been shown capable of transmitting the dis-

ease under laboratory conditions^{33, 39}

These observations make it possible to explain the epidemiology of equine encephalomyelitis, but it must be stressed that there are still many gaps in the evidence and that other possibilities must be considered. For instance, Syverton and Berry^{40, 48} have shown that the gopher or ground squirrel is susceptible, that the tick is capable of transmitting the disease, and that the offspring of infected ticks are themselves infected.

Russian Encephalitis The form of encephalitis occurring in the spring and summer in Russia and reported from the laboratories of Smorodintseff^{21, 22, 23} by a group of collaborators seems to have the following characteristics:

- 1 It is endemic in the forest regions and is limited to people working in the forests
- 2 It seems to remain in the endemic areas without spreading from them
- 3 It does not show the higher mortality in older age groups characteristic of the St. Louis and Japanese encephalitis
- 4 Rodents in endemic areas are infected. Some of them show no apparent illness, and the virus appears in the blood stream
- 5 Ticks in endemic areas are infected and are capable of transmitting the disease
- 6 The virus is serologically related to, but distinguishable from, the virus of Japanese encephalitis

The Russian observers believe that the disease is one of rodents and that man is only incidentally infected.

SYMPTOMATOLOGY AND DIAGNOSIS

The symptomatology and diagnosis of encephalitis are considered at this point rather than earlier, because epidemiological considerations must enter into a differential diagnosis.

von Economo's disease has an acute stage lasting a few days characterized by slight fever, dizziness, diplopia, ocular paralyses, and sometimes headache, some stiffness of the neck, and a mild pleocytosis in the spinal fluid, usually about fifty cells. The symptoms are variable and in about half of the cases are so mild as to pass unnoticed or not to suggest encephalitis. It may be months or even years later that the sequelae (or more correctly the chronic stage) make the diagnosis evident.

The course of the disease, although variable in the extreme, classes

patients logically into the following groupings, according to Josephine Neal 1 those that make a complete recovery, 2 those in whom the disease is progressive, 3 those in whom there is progression of the disease after some delay, and 4 those in whom the disease progresses with remissions

In the chronic stage, contractures, spasticity, mental deterioration, and Parkinson's syndrome are particularly characteristic

The other types of encephalitis discussed are so similar in their clinical manifestations in the acute stage that they may be considered together Although there may be a short period of invasion, the onset is usually sudden, with fever, headache, occasionally vomiting, stiff neck, and pleocytosis in the spinal fluid, usually in the neighborhood of 200 to 300 cells Mononuclear cells predominate, except apparently in equine encephalomyelitis where neutrophiles¹³ seem to be preponderant

Differentiation may be made on the following points

- 1 Only St Louis encephalitis and equine encephalomyelitis have been recognized in the United States
- 2 The highest incidence of these diseases is in the late summer and fall
- 3 Specific neutralizing antibodies may be demonstrated after recovery
- 4 Virus may be isolated from the central nervous system of fatal cases and may be identified
- 5 Serious sequelae are rather rare after St Louis encephalitis, but common after equine encephalomyelitis
- 6 Older people are particularly susceptible to St Louis encephalitis, this is not true of equine encephalomyelitis

It should be emphasized that on clinical grounds alone a positive differentiation of the different forms of epidemic encephalitis is not possible It is only with the aid of the laboratory that this may be accomplished

There are other forms of encephalitis, for example, postinfectious encephalitis, and other infections of the central nervous system, which may confuse the diagnosis These must be differentiated in making the diagnosis, but are not considered in this paper

TREATMENT

Treatment of all the infections included under the generalization "epidemic encephalitis" is symptomatic Lumbar puncture frequently

relieves headache, and sedation may be necessary. Relief of the distressing manifestations of the chronic stage of von Economo's disease has been most successful following administration of belladonna derivatives, particularly in recent years, Bulgarian belladonna, sometimes called *bella bulgara*. Many other therapeutic measures have been tried with varying opinions concerning their value.

PROPHYLAXIS

Prophylaxis, in the absence of specific immunizing agents, must depend on general measures. It seems reasonable to isolate patients during the acute stages, to restrict visiting, to have attendants wear masks, to disinfect bedding, discharges, and dishes, and to screen rooms. Screening seems particularly justifiable in areas where equine encephalomyelitis is present in animals. Vaccination of horses against equine encephalomyelitis with formalinized chick embryo vaccine appears to be of value, in man this vaccine has been used with apparent success in laboratory workers intimately exposed to the virus. It is too early to state whether the use of the vaccine under field conditions is advisable.

SUMMARY

Epidemic encephalitis must now be considered a general term embracing a number of etiologically distinct infections of the central nervous system which must be identified individually for diagnosis. Since all are so similar epidemiologically, clinically and pathologically, their differentiation is possible only with the aid of the laboratory where etiologic studies or neutralization tests can be carried out to establish the diagnosis. The manner of spread of these diseases is, for the most part, unknown, but some appear to have a reservoir in lower animals and to attack man through the bites of insects.

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PROGRESS IN THE PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH LESIONS OF THE BILIARY TRACT*

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I SHALL confine my remarks this evening to certain aspects of the pathologic physiology of the liver, with which we have had some experience during the past few years. Because of the intimate relationship of cholecystitis and hepatitis, there is frequently some hepatitis present before the effect of ductal occlusion from stone still further damages the hepatic cells. That extensive hepatitis may coexist with simple gall-stone disease is not so generally accepted but it is nevertheless true. The occlusion of the common bile duct by a stone is further complicated by the fact that in most instances the gall bladder is at that time moderately or severely damaged. Under such circumstances the failure of the gall bladder to concentrate the trapped bile for a period leads to a rapid increase in the extra- and intrahepatic bile pressure so that hepatic secretory suppression occurs at an earlier period after obstruction.

The opportune time, therefore, to operate on a patient with gall stones is early when the stones are still present in the gall bladder and when the patient is suffering from the classical dyspepsia, or colic, or both, of simple calculous disease. It is, moreover, of importance to remove any calculi from the common duct at the primary operation. The time honored concept that a previous history of jaundice is the indication for common duct exploration has too frequently resulted in the primary or secondary operation being done following extensive liver injury or even during a period of intense obstructive jaundice, when the risk of operation is greatly increased.

In no field of surgery has the physiologic approach to the problems of preoperative and postoperative care had a greater influence, or saved

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more lives, than in the treatment of advanced biliary tract disease. The high mortality in the past can be ascribed neither to less technical skill nor to poorer surgical judgment, but rather to the lack of information concerning the pathologic physiology of the processes involved and the manner by which they can best be controlled prior and subsequent to operation. The special methods of preparation and after care have been based in large part on experimental studies.

The preoperative preparation of the patient should be directed toward correcting, as far as possible, any existing collateral disease, preventing postoperative hemorrhage, and altering the composition of the hepatic cells so as to prevent further liver injury and to allow for repair. I shall not discuss coexisting cardiac or pancreatic disease except to state that neither of these conditions should be considered as an insurmountable barrier to operation. If the patient is properly prepared for operation, with the help of a competent internist, the added risk of either of these conditions is not great.

Angina pectoris may be mimicked in every way by gall-stone disease. We have had a number of examples of this when stones have been present in the common duct, even though jaundice has never been present. Surely operations on or injections of the sympathetic nervous system should not be undertaken without first subjecting the patient to adequate surgery for the gall-stone disease if this is present and the effort syndrome of angina pectoris is absent.

It is generally believed that hepatic disease is unassociated with renal dysfunction. While in general this may be true, there occurs in a number of patients with obstructive jaundice a serious impairment of the functional activity of the renal parenchyma. It is in this group of patients that a low serum calcium may be encountered, which is nearly always associated with a serum protein deficiency or with hyperphosphatemia. These are even more apt to be present if the patient had pre-existing renal disease. A preoperative high blood non-protein nitrogen in these patients is not always of serious significance for subsequent to surgical therapy the evidences of renal injury may rapidly subside. In the absence of a history of previous renal injury the high blood non-protein nitrogen concentration need not alarm one unnecessarily, unless the entire clinical picture, at the same time, warrants alarm.

The evidence of renal impairment should in the main be considered as an additional load which has been added to that which the patient

is already carrying It must be taken into account in preparing the patient for operation, and in determining the anesthetic to be used for operation Above all, it must be considered in the administration of fluids, especially large amounts of sodium chloride, which may so tax a renal system, which is near the breaking point, as to result in renal insufficiency

The advent of ductal occlusion causes serious disturbances in the physiology of the liver The cells continue to secrete bile until the pressure in the bile ducts equals the secretory pressure of the liver The presence of previously impaired gall-bladder function results in a shorter period of time between occlusion and icterus When the intrahepatic bile pressure reaches from 280 to 330 millimeters, pigment does not pass through the hepatic cells and deep icterus results Any further secretion is from the cells lining the ducts and results in the formation of what is commonly called "white bile "

The increase in ductal pressure which occurs following occlusion causes a retardation of the portal blood flow and thus there may develop local hepatic anoxia in the face of some evidence of an increased oxygen consumption in the liver during obstructive jaundice Since the liver cells are extremely sensitive to oxygen want, further hepatic injury ensues Thus the primary hepatitis, if this was present, is accentuated by the increased pressure in the intrahepatic bile ducts, and by the secondary anoxia The injured liver cell is less capable of holding, and of storing glycogen It rapidly loses its stores of mobile protein and may not normally synthesize protein It is incapable of normally metabolizing the fat which comes to it and there is apt to occur fatty infiltration The latter process is more apt to be excessive when there is considerable fat in the subcutaneous tissues

While it was previously believed that the liver glycogen protected the liver against injury during anesthesia, information which we have obtained leads us to state that it is the liver fat which conditions liver necrosis subsequent to the use of volatile anesthetics The increase of the liver glycogen is valuable, therefore, only if by increasing the liver glycogen, liver fat is reduced, that is, if the reciprocal relationship between glycogen and fat described by Rosenfeld is fulfilled It is also probable that an adequate amount of hepatic glycogen will, to a degree, protect the protein stores of the liver Observations which we have made on the dog and on a series of patients with serious hepatic injury, who

were prepared for operation by a high carbohydrate diet and the intravenous administration of glucose for from eight to fourteen days prior to operation, force me to state that often there remained in the liver concentrations of fat which might have resulted in further serious liver injury, had a volatile anesthetic been used

The plan which we are now using is as follows. The patients, if they can be made to eat, are given a diet which consists of 75 to 80 per cent of their calories as carbohydrate to which is added protein in an amount of 20 per cent of the total calories. The diet is given in small amounts but at frequent intervals, so that the total caloric intake is, if possible, about 3,000 calories per day. The protein is added because it assists the carbohydrate in reducing the hepatic lipid concentration, it aids in the prevention of injury by certain hepatotoxic agents, and, furthermore, unless sufficient stores of protein are present, tissue regeneration cannot take place. In addition to the carbohydrate-protein meal we give these patients approximately 10 milligrams of crystalline vitamin B₁ and a varying amount of desiccated bile daily. With such a method we have increased the liver glycogen concentration in the presence of complete ductal occlusion in the experimental animal to as much as 12 per cent, a concentration which previously we had thought unattainable, and we have simultaneously reduced the liver fat from levels as high as 50 per cent to a normal level over a period of one week.

The use of substances containing vitamin K₁ or K₂ or of the synthetic quinone derivatives having a K-like action has made postoperative hemorrhage an exceedingly rare complication. In doses of 2 milligrams, three times a day, 2-methyl-1,4-naphthoquinone is effectual in restoring a normal prothrombin time in the great majority of patients within 72 hours. It is even more potent than the naturally occurring vitamin.

The hemorrhagic tendency of the jaundiced patient is due to a prothrombin deficiency conditioned by the absence of bile salt from the intestinal tract. When the vitamin K substrates and synthetic substitutes are used bile salts should be used with them. The soluble synthetic K substitutes can be used intravenously.

All severely jaundiced patients who have not responded to K therapy are placed on a forced diet and are transfused prior to operation. Our practice has been to use small amounts, 250 to 300 cubic centimeters of blood, for two or three days before the contemplated exploration. This serves several purposes. It improves the quantity and the

quality of the blood, it provides serum protein which may be deficient, and it improves the oxygen-carrying capacity of the blood

We have come to believe that early operation, once occlusion has occurred, is not always to be desired. It has been our policy to withhold operation when the bilirubin concentration in the serum is increasing or decreasing. If it is increasing or decreasing, we wait until the concentration reaches a plateau. During this period the patient is being prepared for operation. Except where suppuration is suspected, the operation is safer when hepatic function has stabilized itself against a high or low serum bile pigment concentration and an adequate program of therapy has been carried out.

In the light of available evidence we believe that the anesthetic of choice is spinal anesthesia. We have good evidence that ether may cause serious liver injury in the presence of the conditions often existing during ductal occlusion. Nitrous oxide and oxygen, when pushed to the point of even semi-satisfactory relaxation, causes an anoxia which results in further liver injury. Cyclopropane may be satisfactory but there is as yet insufficient evidence as to its effect on the hepatic parenchyma, especially in the presence of high concentrations of hepatic lipid, to warrant its widespread adoption.

Spinal anesthesia, in which marked depression of the blood pressure is prevented by the preanesthetic administration of adequate doses of ephedrine, has proven so satisfactory in our hands that until a better method is demonstrated we shall continue to use it. Carefully administered, it is, we believe, the safest anesthetic in these bad risk patients.

We believe that the subcostal incision affords better exposure of the biliary passages, is associated with less postoperative pain, fewer pulmonary complications and a lower incidence of postoperative herniation than any other incision. Its full advantages are never appreciated until it is used.

I shall not discuss the various technical details necessary to complete the operation satisfactorily. In the presence of stone obstruction a thorough search is essential and the removal of a single stone is not sufficient reason for terminating the exploration. Not until the operator is satisfied that there are no stones in the right or left duct and a catheter can be freely passed into the duodenum is his responsibility for further exploration at an end.

As soon as the opening in the common duct is closed around the tube,

fluid is introduced through the open end of the tube and the tube is then clamped. When the patient is returned to his bed the free end of the tube is attached to a "decompression" apparatus and this is so arranged that the top level is kept at approximately 200 millimeters above the common duct. Over a period of days this is gradually lowered but it is never lowered to the point where large amounts of bile are permitted to drain externally.

The use of this principle serves several useful purposes. In the first place, it prevents an acute hepatic hyperemia subsequent to release of the ductal occlusion. After the sudden release of a complete ductal occlusion there is often observed an intense hyperemia of the liver tissue and the extravasation of large amounts of blood in the perivascular spaces. Although decompression occurs in part during the operation, the maintenance of an adequate pressure level thereafter is, we believe, of real help in preventing massive extravasation of blood into the liver tissue. Furthermore, it overcomes the defect of the older method of drainage into a bottle at the bedside in that large amounts of bile are not sucked into the container. This added advantage of permitting the bile to enter the intestine at an early period is obvious. The fluid and electrolyte balance is more easily maintained and the extrahepatic functions of the bile are reestablished within a short time after operation. The effects of excessive external bile drainage were described some years ago by William Halsted who personally experienced them. The lassitude, weakness, anorexia, rapid pulse and even comatose state so frequently observed in such patients can in large measure be prevented by the use of the "decompression" principle. The additional advantage of the bile subserving a useful intestinal function I shall describe later.

No tube should be removed from the common duct before a cholangiogram has been made. Even the most experienced of surgeons will occasionally leave a stone behind. The time to know this is before the "T" tube is removed. It is then that the Pribram method may be used with some hope of success.

In the administration of fluid during this period one must be guided by the principles laid down by Wiley and Newburgh and their elaboration by Collier and Maddock. The control of the postoperative administration of intravenous fluids to these patients is not to be left to one of a group of constantly changing interns, nor can the quantity or type be determined routinely for all patients.

As soon as the stomach is retentive, food should be given by mouth. The diet which we have used in the postoperative period is again a carbohydrate-protein mixture, practically devoid of fat. With such a regime regeneration of liver cells may occur rapidly and normal function, if this can be restored, will make its appearance at an earlier period than when the patient is on a haphazard diet or on a regime which restricts food by mouth beyond the necessary period. It is not possible to furnish the energy requirements of the patient and increase the liver glycogen and protein storage by intravenous therapy. Protein wastage will be prevented, liver glycogen stores will be built up, liver fat displaced, and cell regeneration take place when the total food intake is more than sufficient to cover the energy requirements. Data which we plan soon to publish lend no support to Soskin's concept of a physiological basis for intravenous glucose in these patients.

The restoration of bile to the intestinal tract at an early period by the use of a "decompression" apparatus, if the lower end of the common duct is patent, has already been mentioned. The most important function of the bile is its intestinal function. The activation of lipases, the emulsification of fats and their transport across the intestinal membrane, and the aid in the absorption of accessory food substances, such as vitamins A and K, are but a few of the activities which bile plays in the small bowel.

For some time we replaced part of the bile drained to the exterior through a gastric tube, and still use this method when edema or inflammatory exudate prevent the entrance of bile directly into the duodenum.

With the decompression method bile flows directly into the duodenum. Convalescence is smoother, and we have had an absence of the asthenic states which were so often observed when excessive external biliary drainage occurred. The asthenia which Whipple called, for want of a better name, "pancreatic asthenia" has been rarely observed by us since we began the routine use of decompression nine years ago. It is, we believe, due to a disturbance of intestinal and hepatic physiology and is the result, in part, of an interference with the extrahepatic functions of the bile. Why it makes its appearance in some patients and not in others, and why it is often not observed after prolonged ductal occlusion prior to operation, I cannot explain.

I have discussed a few of the factors which must be considered in caring for these desperately ill patients before, during and after opera-

tion In each of them there are present certain profound physiological disturbances, some of which are understood and others of which remain to be elucidated The risk of operation will be reduced if attempts are made prior, during, and subsequent to operation to restore function to as nearly normal as is possible Such a program has resulted on my service in the Hospital of the University of Pennsylvania in a very desirable reduction in the morbidity and mortality of operations on these seriously ill patients Further improvement in our immediate and late results will come from a fuller understanding of the conditions imposed on the organism in the presence of acute and chronic hepatic injury and the mechanism by which these pathological states may be controlled or corrected prior to operation

THE CHEMICAL AND PHYSIOLOGICAL PROPERTIES, AND CLINICAL USES OF THE CORPUS LUTEUM HORMONE, PROGESTERONE*

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THE corpus luteum hormone, progesterone, owes its discovery to two events. First, a considerable amount of physiological experimentation indicated the production of a special hormone by the corpus luteum, second, after the preparation of active estrogenic extracts it was found that these preparations did not produce the effects characteristic of the corpus luteum.

The first actual experiments to establish the corpus luteum as an endocrine gland were made by Fraenkel¹ in 1903. He found that removal of the corpora lutea in the first few days of pregnancy prevented the continuation of pregnancy. Loeb² in 1907 made the next contribution by showing that the endometrium of the guinea pig is sensitized while under the influence of the corpus luteum so that simple, mechanical trauma at the time when the embryos would be implanting, results in the formation of a decidual tumor at the site of injury. This experiment showed that the endometrium requires the presence of the corpus luteum before it can respond normally to the presence of the embryo. A little later, in 1910, Bouin and Ancel³ showed in the rabbit that the endometrium undergoes marked proliferative changes as the corpus luteum develops, and further, that removal of the corpora lutea prevents this proliferation. Here then was the first evidence that actually the embryos in Fraenkel's experiments arrived in a uterus which was not prepared by the action of the corpus luteum to receive them. Coincident with the growth of the corpora the endometrium proliferates rapidly, as we now know because of the action of progesterone, and the embryos survive. If the corpora are removed, this proliferation does not take place and growth of the embryo stops, as was shown by Corner⁴ in 1928, as soon

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as it reaches the uterus. This proliferation is essential for the implantation of the embryo, and hence has been called progestational proliferation.

Alterations of the endometrium of similar significance are found in association with the growth of the newly formed corpus luteum in all species that have been investigated, and in the woman we now know that the premenstrual changes are due in part at least to the progesterone produced by the corpus luteum. Such alterations, no matter how dissimilar they may appear to be in different species, are essential for the safe implantation of the embryo.

The corpus luteum hormone, of course, has many properties other than those specifically pertaining to the uterus but they are presumably all related to the problem of preparing the body for pregnancy and the safe continuation of pregnancy.

None of the specific effects of the corpus luteum can be satisfactorily and completely produced by estrogens. Pregnancy cannot be maintained in a castrated rabbit with estrogen. The endometrium of the guinea pig cannot be sensitized by estrogens. Premenstrual changes cannot be produced in primates with estrogens. For these reasons, George Corner and I began our work on extracts of the corpus luteum.

To study the effect of a corpus luteum extract, it is necessary only to castrate the rabbit about eighteen hours after mating, and then to give the preparation to be tested for five days to see what effect it will have on the endometrium and on the embryos. If the extract contains no corpus luteum hormone, the endometrium shows no progestational proliferation and the embryos do not develop, if on the other hand the extract contains corpus luteum hormone, the uterus undergoes typical progestational changes and the embryos develop exactly as in normal pregnancy, even though the rabbit has been deprived of her own corpora lutea almost from the time of ovulation.

This method of testing the extracts enabled Corner and myself to prepare active crude extracts of the corpus luteum. These crude extracts produced progestational changes in the endometrium, maintained pregnancy to term in castrated rabbits and sensitized the guinea pig's endometrium so that deciduomata could be produced experimentally. In short, these crude extracts contained a hormone (or hormones) which did all the things that the corpus luteum was supposed to do, at least in so far as the rabbit and guinea pig are concerned. Because of its

obvious relation to pregnancy, it was named progesterin, i.e., a substance necessary for pregnancy

The active principle was independently isolated in 1934 by Butenandt,⁵ Slotta, Ruschig and Fels,⁶ Allen and Wintersteiner,⁷ and Hartmann and Wettstein.⁸ It was found to be a neutral compound, a diketone with the empirical formula $C_{21}H_{30}O_2$. This immediately suggested that it was closely related to pregnandiol, a dialcohol previously isolated by Marrian⁹ in 1929 from the urine of pregnant women, with the formula $C_{21}H_{36}O_2$, the detailed structure of which had already been established by Butenandt.¹⁰ The supposed relationship was proved soon by Butenandt by the preparation of progesterone from pregnandiol and from stigmasterol. It has since been prepared from cholesterol and sarsapogenin and possibly other sterols.

Progesterone is soluble in most organic solvents, and in vegetable oils, such as sesame oil, olive oil and peanut oil, but it is insoluble in water. It is ordinarily dissolved in a bland vegetable oil and is given by intramuscular injection. Despite its insolubility in water, absorption from the oily solutions is quite rapid. The effect is not prolonged and anyone who has had much experience with the use of progesterone in animals gives little credence to reported remarkable clinical results where small doses were given once weekly. For example, in certain experiments in rabbits the omitting of a single daily dose may be sufficient to disturb a pregnancy being maintained artificially by progesterone. In women, too, progesterone deprivation frequently is followed by menstrual bleeding within forty-eight hours. If one is attempting therapy with progesterone, injections should be given each day. In this respect it is quite different from the esters of estradiol and testosterone, the absorption of which extends over a period of several days.

The conditions for which progesterone may be used in women are probably rather few but before discussing them it may perhaps be profitable to mention some of the physiological effects in animals. The endometrium of the rabbit responds to progesterone the same as it does to action of the rabbit's own corpora. Pregnancy can be maintained to full term in the absence of the ovaries, and delivery can be prevented by continued administration of adequate amounts. It sensitizes the endometrium of the rat and the guinea pig so that deciduomata can be produced experimentally. In short it substitutes completely for the corpus luteum, except that for some types of response estrogen must be given

at the same time, i e , some physiological responses attributed to action of the corpus luteum are in reality due to combined action of estrogen and progesterone

Progesterone also has a specific action on the uterine muscle. It is well known from the experiments of Knaus¹¹ that the reactivity of the rabbit's uterus to pituitrin is materially changed during pseudopregnancy or pregnancy. If a segment of the uterus is removed from an animal in heat and suspended in a suitable saline bath, spontaneous contractions occur and can be recorded by means of a kymograph. If now a small amount of pituitrin is added, there is an immediate and prompt response, shown by a typical tetanic contraction. A similar response is, of course, obtained in the human uterus at the time of delivery when pituitrin is given. This sensitiveness to pituitrin in the sexually mature rabbit is always present when no corpora lutea are present in the ovaries. If functional corpora are present, as in pregnancy or pseudopregnancy, the uterus similarly studied *in vitro*, is not responsive to pituitrin. The uterus is refractory. This pituitrin-inhibition, as it is called, is due to the action of progesterone and can be produced experimentally by giving rabbits 10 mgm of progesterone daily for five days (Makepeace, Corner and Allen)¹²

In vivo studies carried out by recording the uterine motility in anesthetized rabbits by means of an intrauterine balloon show too that progesterone has a quieting effect on the uterus. It has been shown that estrogen induces strong, rhythmical contractions and that progesterone brings about quiescence (Allen and Reynolds)¹³. The effects are noticed rather quickly, indicating prompt absorption, even though the hormone is dissolved in an inert vegetable oil. It is this quieting effect on the myometrium which has led to the use of progesterone in dysmenorrhea, threatened abortion and premature labor.

The effects on the endometrium of the primates are of even greater interest because it has now been amply demonstrated that the cyclic changes which are known to occur in the corpus luteum phase of the cycle can be produced experimentally by the use of progesterone. The exact details of dose are not as well worked out as in the rabbit but several observers have produced premenstrual changes in both monkeys and women with progesterone.

The menstrual cycle of the primate is inseparably associated with the corpus luteum, whenever the cycle is ovulatory, but to complicate

matters, many cycles in monkeys are anovulatory and we have fairly good evidence that many types of abnormality in the human cycle are accompanied by and probably due to disturbances in the mechanism of ovulation. The types of cycles can be best explained by discussing the methods of inducing artificial menstruation.

Menstrual bleeding can be produced experimentally in both women and the lower primates by either of two mechanisms. If a castrated individual is given estrogen for a short period of time, say two or three weeks, the endometrium responds by moderate growth. If the hormone is then discontinued, vaginal bleeding similar to menstruation occurs, beginning about seven to ten days after the last injection. This bleeding is called estrogen-deprivation bleeding. The amount of estrogen necessary to produce this depends on the particular preparation used. With estradiol benzoate, for example, it requires 15 to 20 mgm per week.

Before passing on to the second mechanism of producing bleeding, it may be well to dwell on the significance of this observation. Since bleeding can be produced with this one hormone alone, it becomes obvious that some menstrual cycles might actually occur because of this same mechanism. Follicles may grow, produce estrogens and then, without ovulation having occurred, undergo atresia. The estrogen level falls and bleeding occurs because of estrogen deprivation. This is obviously not a complete cycle because there has been no ovulation, hence, no corpus luteum, and therefore the endometrium does not progress to the premenstrual or secretory type. This type of cycle, called an anovulatory cycle, was described first in the monkey by Corner. This was considered by many gynecologists, both in this country and in Europe, an interesting peculiarity of the monkey, but of no significance as far as the woman was concerned. Such is certainly no longer the case and many cycles in women are undoubtedly anovulatory. One of the first evidences of ovarian dysfunction is failure of ovulation.

Estrogen-deprivation is not the only method of producing menstruation experimentally. It was soon found that administration of progesterone would prevent estrogen deprivation bleeding. If a monkey is given estrogen, and then if progesterone is given, beginning as soon as the estrogen is stopped, no bleeding occurs. However, when the progesterone is discontinued typical bleeding occurs. Progesterone, therefore, prevents estrogen-deprivation bleeding, but its withdrawal leads to pro-

gesterone-deprivation bleeding. This means that bleeding can be due to two different types of endocrine change. Externally the bleeding is the same, but the type of endometrium from which the bleeding occurs is quite different in the two cases. In the estrin stimulated endometrium, bleeding occurs from an interval type of endometrium, whereas in the estrin and progesterone stimulated endometrium, bleeding occurs from a premenstrual endometrium.

A final way of producing bleeding probably nearly approximates the mechanism present in the normal ovulatory cycle. If a monkey be given an adequate amount of estrogen continuously, it is possible to produce menstrual bleeding simply by the administration of progesterone for a few days. Bleeding occurs two to three days after the last injection. This means that bleeding will occur whenever the progesterone level falls, regardless of the amount of estrogen present, within certain rather wide limits (Corner) ¹⁴

An interesting variant of this experiment has been recently carried out in women by Zondek ¹⁵ He has shown that administration of progesterone to a normal woman in the first half of the cycle leads to bleeding 48 to 72 hours after the last injection without at the same time necessarily preventing the appearance of the next normal menstrual period at the expected time. This only serves to emphasize the point that progesterone-deprivation is followed by bleeding provided the stimulation has been sufficient.

By way of confusing the issue it might be appropriate to point out what is already probably obvious to you, namely, that bleeding can occur from almost any sort of endometrium. The degree of development of the endometrium depends on the amount and duration of action of the two ovarian hormones but the bleeding occurs from hormonal deprivation (except possibly in hyperplasia), the stage of development of the endometrium being incidental and in no direct way related to the cause of the bleeding.

The final question is, what clinical uses can be made of the various physiological properties of progesterone?

Progesterone may be used in dysmenorrhea, the theory being that the pain is due to ischemia resulting from strong contractions of the uterus. Progesterone does relax the uterine muscle in both animals and humans and hence, should be beneficial in dysmenorrhea. The general opinion, I think, is that about one-half of the cases of dysmenorrhea are

benefited My own experience has not been extensive, but in several patients there can be no doubt but that marked improvement was noted The progesterone has to be given before the period has begun and I have had the best success when 10 to 20 mgm was given intramuscularly on the last three days immediately preceding the flow I have got the impression also that it is the progesterone given in the last 24 hours before the onset which produces the effect Unfortunately the treatment is not curative in any sense of the word since the next period is usually as bad as ever

Threatened abortion is, of course, theoretically the indication par excellence for progesterone Excision of the corpus luteum of pregnancy results in abortion in most mammals (including the human in early pregnancy) and, experimentally, progesterone will maintain pregnancy normally following excision of the corpora Transfer of this information to the human is not so justifiable, however, because there is very little evidence that abortion is necessarily due to corpus luteum deficiency In many instances it may be and probably is due to corpus luteum deficiency but this is frequently due to the presence of a defective embryo in utero The administration of progesterone to such a case, of course, might defeat the natural process of expelling the defective embryo I have seen one such case where the abortion was prevented on two different occasions only to have a defective embryo expelled at the fourth month in which the placenta and membranes were intact but without a fetus In case of a threatened abortion in which the bleeding is slight and the uterus of normal size and consistency for the period of amenorrhea, progesterone is, of course, indicated It can do no harm and it may be beneficial

The question of dose is paramount In normal pregnancy at the third month 10 to 20 mgm of pregnandiol are excreted daily (Venning)¹⁶ If this be taken to indicate the amount of progesterone metabolized, it is obvious that 5 to 10 mgm as a minimum should be given daily until the symptoms have subsided, i e, for a week or so It seems probable that some abortions may occur because the placenta does not begin elaborating sufficient progesterone quite soon enough, and if this be so, then progesterone given for a short time might be expected to give good results

Habitual abortion is also considered an indication for progesterone This is a rare condition and some of these cases will occasionally carry

a fetus to term after many previous miscarriages with no treatment. Many patients will have two or three spontaneous miscarriages only to have the following pregnancies progress normally. It is very difficult, therefore, to evaluate the beneficial results reported in the literature, especially since the doses used have usually not been large. In habitual abortion progesterone, if used at all, should be started almost as soon as pregnancy can be diagnosed and it should be continued probably to the fourth or fifth month, the reason for beginning early being that the fetus may fail to develop normally if the progesterone level is inadequate. In the rabbit progesterone deficiency in early pregnancy leads to defective development and early death of the embryos.

Functional bleeding is one condition worth special consideration. Amenorrhea or bimonthly bleeding usually do not impair the health, but continuous bleeding leads to considerable ill health, and rarely death has occurred from blood loss due to functional bleeding. The exact cause of the bleeding is not known. It is reasonably certain, however, that ovulation is not occurring and hence that progesterone is not acting. The use of pituitary hormones for this condition is based on the assumption that ovulation may be induced, and a normal cycle established. This can rarely be accomplished by this means. There is one other method of approaching the problem that is often successful. This involves the use of progesterone. As I mentioned earlier, progesterone has the property of preventing estrogen-deprivation bleeding and also of preventing the onset of normal menstrual bleeding, if given in adequate amount. It is logical, therefore, to try it, especially since continuous functional bleeding and hyperplasia are presumably associated with progesterone deficiency. There is an added reason. Some investigators believe that hyperplasia and the associated bleeding are due to hyperestrogenism. If so, progesterone is the natural hormone to use because there is ample evidence indicating that progesterone reduces or at least alters the effect of estrogens.

We (Allen and Heckel)¹⁷ have given progesterone to several adolescent girls with more or less continuous bleeding with rather uniform results. The general plan has been to give progesterone intramuscularly, 2 to 10 mgm daily, for from five to ten days. Ordinarily the bleeding decreases markedly after the second and third dose but a small amount of brownish discharge may persist. When the injections are discontinued, the bleeding may recur within 48 to 72 hours and persist

for four or five days, resembling in every respect a slightly profuse menstrual flow. Bleeding does not invariably decrease when progesterone is given. Occasionally the spotting or even moderate bleeding may continue during the course of injections but usually cessation of injections is followed by increased bleeding. In every instance where this result has been obtained the flow has stopped completely after a few days. This bleeding is probably a true progesterone-deprivation bleeding. Bleeding may occasionally increase during the course of injections. The reason for this is not clear at present but there are so many peculiarities about bleeding that one can only record the observation and await the explanation. For example, I have seen bleeding occur in a castrated woman receiving estrogen daily, during a course of injections of progesterone, hence with no deprivation of either hormone. In other cases, usually when the smaller doses were given, the bleeding has stopped but there has been no recurrence as a result of the withdrawal of progesterone.

These results, by themselves, are of considerable interest but the subsequent course has been even more interesting. In most instances several fairly normal periods have followed the progesterone therapy. The first patient treated by this scheme was given crystalline progesterone in 1935. She was fifteen years old and had had continuous bleeding for two months. She was given 20 mgm daily for five days and the bleeding stopped. Menstrual periods began about a month later and have been quite regular ever since. Another patient of seventeen years who had been bleeding daily for two years, was given 5 mgm daily for six days. The bleeding stopped after the third injection. A copious menstrual period began two days after the last injection and lasted five days. During the next six months the periods were somewhat irregular but there were no prolonged periods and there was no episode of prolonged bleeding. I cite these two only as examples of what has occurred. In some cases there has been a recurrence of functional bleeding after several months of normal cycles, but the same beneficial results were obtained by a second course of progesterone.

The beneficial effects in functional bleeding from progesterone should not be permitted to obscure the fact that functional bleeding is a manifestation of ovarian dysfunction. As such it may indicate hypothyroidism and many patients with functional bleeding have been permanently relieved by the use of thyroid.

Amenorrhea, one of the most troublesome types of endocrine dysfunction when it is not amenable to thyroid extract and improved nutrition, provides another type of disturbance in which progesterone may be used. In view of the observation that the vicious cycle of continuous bleeding may frequently be broken by progesterone, I have tried it in several cases of amenorrhea in which there was no marked atrophy of the reproductive organs. In several cases the administration of 5 to 10 mgm daily for six days was followed by menstrual bleeding, the onset being 48 to 72 hours after the last injection. One of these cases treated recently had had no menstrual periods for two years and had failed to menstruate following the use of equine chorionic gonadotropin, and human chorionic gonadotropin and had proved intolerant to thyroid extract. Two menstrual periods were induced by the use of progesterone, following which a normal period occurred. Another patient who had not menstruated for one and one-half years bled for four days after only three injections of progesterone. I cite these observations only to show that bleeding can be induced in amenorrheic individuals as a result of progesterone deprivation. Estrogen deprivation also is followed by bleeding in amenorrheic patients but it is practically never followed by normal cycles. It seems too much to hope that cycles produced by progesterone deprivation would be followed by normal periods but at least it can be no more of a failure than most of the other hormones that have been used.

There is one other compound closely related to progesterone which I shall mention. This compound is ethinyl testosterone (anhydro-hydroxy-progesterone, pregnenolone). It was prepared originally by Inhoffen and Hohlweg¹⁸ in 1938 and was shown to be a compound with progesterone-like properties when given by mouth. This compound is far less active by mouth than is progesterone intramuscularly but it is much more active by mouth than is progesterone by mouth in the rabbit. In the guinea pig, however, Soderwall¹⁹ (1940) has recently shown that progesterone and pregnenolone have about the same activity, the oral dose of either being about 20 times the injected dose of progesterone. This compound is also mildly estrogenic and mildly androgenic.

The indications for use of pregnenolone are the same as those for progesterone. It produces nausea occasionally but it is probably non-toxic in doses of even 100 to 200 mgm per day for a period of two weeks or so. A recent report by Cohen and Stein²⁰ (1940) indicates that

it may be toxic in rats, hence caution must be observed in its use

In conclusion it is proper to emphasize that the corpus luteum hormone has a firm place in the physiology of reproduction, and our appreciation of its many properties helps us to approach disturbances of ovarian function more rationally. It does not serve as a "cure-all" for any of the dysfunctions of the ovary but it is another tool which can be used in attempting to ascertain the cause of such disturbances. If used with that in mind the results are bound to be instructive.

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CHEMICAL, PHYSIOLOGICAL AND CLINICAL
ASPECTS OF THE ANDROGENS*

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An extensive appreciation of the physiology of androgens dates from the chemical isolation of pure hormones, only a few years ago, 1933-35. In this brief period biochemists and physiologists have published a vast number of experimental observations on some sixty-odd pure chemical substances with androgenic properties, some prepared from sterols, some derived from animal tissues, still others derived from urinary extracts^{1,2}. It may be well to pause for a moment to define the term androgen. Technically, an androgen is a substance which induces masculine qualities or characteristics. But what shall be our criterion of a masculine characteristic?

All sorts of ingenious tests have been devised for the measurement of the "male-producing" qualities or, in other words, the androgenicity of compounds. The two most common methods, as is well known, are based upon the effects of the test substance on either the internal genitalia (prostate and seminal vesicles) of spayed animals or on some external masculine organ (such as the comb) of spayed birds. The capon's comb-growth and the weight of the prostate of the spayed rat are the tests in most frequent use today. All sorts of modifications of these fundamental basic tests, however, are practiced. For example, somewhat different effects may be noted from variations in the method of administration of the substance to be tested, i.e., whether fed, injected or applied directly to the test organ by incision. Further variables are found when esters are made of the test substances, due to alterations in the time of absorption. The same is true of variations of the medium in which the test substance is administered. The response of one animal species may be quite different from that of another, there may be different responses depending on the age of the animal, the season of the year and many other factors.²

* Read January 2, 1941 at the Annual Meeting of The New York Academy of Medicine.

It is unnecessary to delve more deeply into these matters at this time, they are mentioned mainly to recall and emphasize how much care must be taken when we are attempting to interpret the results of any given experiment with androgenic substances

As the result of experiments on lower animals, testosterone seemed the most logical androgenic steroid with which to furnish clinicians for extensive study in man. Because of its rapid absorption and also rapid destruction in the pure form, an ester was used and an oily medium, both of which retard absorption rates. The first extended clinical trials were, therefore, made with testosterone propionate in sesame oil, injected intramuscularly or subcutaneously. Since that time, some four or five years ago, various other methods of administration of testosterone have been tried clinically, among them the use of esters of testosterone other than the propionate, the use of free testosterone or its esters implanted in the form of hard pellets beneath the skin, administration of testosterone and esters by inunction, oral administration of methyl testosterone and, most recently, by means of absorption of testosterone or its esters dissolved in propylene glycol from mucous surfaces such as beneath the tongue.

Following the endocrine law that an organism is usually hypersensitive to a substance it lacks, eunuchs or hypogonad male patients were first selected for clinical trial, with the expectation, which has proved to be justified, that their responses to androgens would be more vigorous and spectacular than those of normal persons.³ In most clinics a true eunuch is a rarity, and most studies have thus of necessity been performed on patients who are hypogonad for one reason or another—the degree of deficiency varying over rather wide limits, as might be expected. By restricting the study to patients long past the usual age of adolescence (say twenty-five years or over) without any evidence of puberty, one can with reasonable assurance feel that any maturation effects resulting from therapy may be attributed solely to the administration of the drug.

I think it may be fairly said that all workers in this field are now agreed that administration of testosterone *to this type of patient* results in certain definite changes to be described, differences of opinion being restricted to optimal dosage, method of administration or the ester to be used, etc.

The more dramatic and tangible physiological effects to which I

refer may be briefly set down as follows enlargement of the phallus, scrotum, prostate and seminal vesicles with production of normal adult prostatic secretion, stimulation of pubic and axillary hair as well as that of the extremities, face and torso, cracking and deepening of the voice and enlargement of the larynx, an indefinable but definite change in the texture of the skin with more "life" and increased secretion of sebum ^{4, 5, 6, 7, 8, 9} On the metabolic side, there is decreased urinary excretion of water, sodium, chloride, potassium, phosphorus and nitrogen, indicating probably active cellular proliferation with addition of true cellular mass ^{10, 11} Retention of these substances is of greater magnitude than could reasonably be accounted for by the growth of the specifically "sexual" structures mentioned previously and is probably participated in by the muscles and internal organs such as the liver Evidence of this is furnished in animal experiments, ^{12, 13} and we have been impressed with the increase in the muscles and proven strength in our patients In addition to these tangible changes certain subjective effects are uniformly noted, namely more vigor with less easy fatiguability, production of increased phallic sensitivity with more frequent erections, induction of the ability to have coitus with ejaculation and orgasm and, less tangible still, a general improvement in the sense of well being ^{7 14}

In the castrate and those with primary gonadal deficiency there is brought about reduction of the excess pituitary gonadotropic hormone ^{16 10} Increases in the basal metabolic rate have been noted, especially when large doses of testosterone have been used ¹⁷ These are by no means all of the changes noted, some others will be mentioned later in the more detailed discussion of certain phenomena

As previously mentioned, it may be fairly stated that all workers agree on the above effects when testosterone is given in adequate dosage to the hypogonad male, and, with some variation in degree of responses, this is true whether his hypogonadism is primary or secondary to pituitary deficiency ¹⁰ Metabolic effects similar in kind though less in degree have also been noted when testosterone propionate was given to normal adult men and to two normal women ¹¹

In the beginning of our own experiments with testosterone propionate in sesame oil given subcutaneously, we arbitrarily chose a dosage of 25 mgm twice per week This dosage seemed to work so well that we continued it over a period of eighteen months in practically all patients treated by this method ^{5 14} Allowing for certain deviations due to varia-

tions in the degree of gonadal insufficiency previously mentioned, the time-relationship and degree of responses elicited followed a surprisingly constant pattern. For example, the patients noted a subjective response of increased phallic sensitivity from the first to the eighth day after beginning therapy (average five days), vocal changes were noted from the twenty-first to the ninetieth day (average thirty days), definite enlargement of prostate and vesicles could be palpated from the eleventh to the sixtieth day (average thirty days), appreciable increase in pubic hair appeared from the thirtieth to the sixtieth day (average forty days), and measurable amounts of secretion could be recovered from prostatic massage from the thirtieth to the sixtieth day (average forty days) *

We have accordingly used this pattern of effects and time-relationships (which we shall hereinafter refer to as our "primary pattern of response") to evaluate the effectiveness of other androgenic preparations and other methods of administration.

We do not mean to infer that the injection of 25 mgm testosterone propionate twice a week is the correct or optimal dose of this substance. As a matter of fact, were we to use this material today, we should advise slightly smaller doses of, say, 15 to 20 mgm, to be given three times per week to avoid the fluctuation of subjective effects which usually occurs when the material is administered at three or four day intervals. We shall discuss this later in dealing with optimal dosage.

The introduction into the subcutaneous tissues of crystalline testosterone pounded into hard pellets was next tried¹⁴ according to the method of Deanesly.¹⁸ The amount of the drug absorbed may be measured by periodic removal of the pellets and reweighing. One would naturally expect variations in the rate of absorption of such pellets depending on their size, surface area and on the degree of hardness. This is undoubtedly the case to a certain degree, but we have found a rather surprising uniformity in the absorption rate, at least until the pellets get very small. There is a vigorous foreign body reaction around the implanted pellets and a thick fibrous capsule is formed.¹⁹ Within this capsule, in the case of testosterone, is a layer of thick gelatinous material looking not unlike pus, for which we at first mistook it. We have repeatedly cultured such material with sterile findings and examined it under the microscope where it looks like amorphous debris. We con-

* The time of noting these changes after beginning therapy is necessarily somewhat vague. We followed the patients as closely as we could, but it was obviously impossible to examine them daily. Since many of the patients were from other cities, we were forced to obtain these data from personal diaries.

cluded that the material consisted of testosterone, extracellular fluid and products of cellular breakdown

This extra layer of amorphous liquid surrounding the pellet, rendering the surface area of absorption, of course, many times larger, and probably shrinking relatively little as the substance of the pellet is depleted, may perhaps be the explanation of the surprisingly uniform absorption rates of pellets of the same size and the small differences in absorption rates of pellets of different size. If pellets of pure testosterone are implanted of such size that they will yield 3 to 4 mgm per day (a single pellet of 500-600 mgm has been found to do this), clinical effects are obtained which correspond closely to our "primary pattern of response." It may be seen that this method of administration, if other factors are equal, effects a considerable saving of material.

We next tried pellets of testosterone propionate. It was found that, for a given pellet of the same weight and consistency, the rate of absorption of testosterone propionate is slightly lower than that of pure testosterone. This may be due to the fact that, although a similar fibrous capsule is found around the propionate pellet, there seems to be less amorphous fluid substance around the pellet, hence the capsule is closer to the pellet itself and there is a decidedly smaller surface area of the capsule. Such an observation is, of course, difficult to prove, but Jewett and Vest, who have implanted and removed all the pellets in our patients, feel that there is no doubt about its factuality.

We have found that if five pellets of 200 mgm each of testosterone propionate—which will yield 3.5 to 5 mgm per day into the circulation—are implanted, our clinical effects can be practically superimposed on our "primary pattern of response."

We have tried only one other ester of testosterone with pellet implantations and in only two cases. This is the dipropionate. In one instance we implanted two pellets weighing approximately 600 mgm apiece and in the other, three pellets weighing approximately 200 mgm apiece. In neither case, after several months' observation, could we detect any appreciable objective or subjective response, and on removal it was found that only minimal amounts of the material had been absorbed (15 mgm in the first case, 10 mgm in the second). Striking also was the fact that practically no amorphous fluid lay around the pellets, the inner surface of the fibrous capsule apparently lying in direct contact with the pellets. This is just like pellets of desoxycorticosterone when removed

Thorn tells me there is no surrounding fluid between the pellets and the capsule.²⁰ We feel that, if enough pellets of dipropionate were administered so that 4 to 5 mgm could be absorbed per day, one would probably obtain good effects and perhaps over a period of two or three or more years. So far it has not been practical to test this hypothesis.

Despite the expressed preference of *every* patient who has tried other methods of testosterone administration mentioned, for the pellet form, it is not entirely free from disadvantages. Out of a series of 125 implants, seventeen have spontaneously sloughed out at varying periods of time. Three out of forty-one implants of testosterone have sloughed, fourteen out of eighty-four of testosterone propionate. Sometimes only one pellet out of the five implanted has been sloughed, in a single patient one pellet may slough at one month, another at three months, and the other three pellets successfully remain without the slightest evidence of irritation, to complete absorption. We have not been able to ascertain that the site of implantation, the depth of the site, the size of the pellet, the type of suture used or any other factor plays the determining role in this sloughing. In no instance has there been any evidence that infection played any role whatever. The tissue forming the capsules around these pellets has been removed and examined microscopically. Our pathologists tell us that there is simple foreign body reaction with many large multinucleated cells but no evidence whatever of any tendency to carcinogenesis.¹⁹

Administration of testosterone and its derivatives by inunction is practicable and perfectly efficacious, as judged by the experience of others.²¹ We have had no personal experience with the method. We suggested its use to a few patients who preferred going twice a week to doctors for injections rather than the daily, time-consuming procedure of rubbing in the drug.

Methyl testosterone has been found in experimental animals far more effective by oral administration than any of the androgenic compounds so far tested clinically. Our own experience with this compound has thus far been too limited for me to state with any assurance its clinical characteristics, and no adequate reports of its use in human beings have come to my attention. Some of our previously untreated hypogonad cases, however, have followed quite closely our "primary pattern of response" when given doses of 25 mgm of this drug per day, others, though the *direction* of response was similar in every instance, seemed to respond

more slowly, as if, in other words, higher dosage would have yielded prompter and more vigorous effects. In two instances, out of our series of thirteen cases, unpleasant side effects, quite similar to those often seen with diethyl stilbestrol, were encountered, necessitating discontinuance of methyl testosterone therapy. Good clinical response was at once attained on substituting pellet therapy in one instance, injection therapy in the other.

To come back to the matter of "optimal" dosage and adequate replacement therapy. If an amount of androgen is administered so as to bring about our "primary pattern of response," is this adequate or optimal? We must confess we do not know, but with the single exception of beard growth—which has never attained normal proportions in any of our forty-odd cases so far followed carefully—the patients are completely satisfied and have expressed the opinion that the replacement was subjectively "adequate."

One might use the urinary androgen excretion as a criterion of adequacy or inadequacy of treatment. With the doses we have used, our patients have in no instance reached the average normal range of 20 to 60 units per day as measured by Fleischmann's rat colchicine technique.²² However, most of those tested have reached what we consider the lower limits of the wide normal variation.

We have recently assayed the urine of our treated patients for 17-ketosteroids* (using Fraser's modification of Callow's method).²³ Our patients have shown well below average normal figures, so that on this basis, too, we should perhaps judge our treatment as suboptimal.

Other workers have given far larger doses than ours and brought about high normal urinary androgen outputs tested biologically,²⁴⁻²⁵ but so far as we can see from their reports, their cases have responded clinically in a manner quite close to our primary pattern. Furthermore, urinary androgen titers are often very poor criteria for the clinical effectiveness of a dose. Dorfman and Hamilton's observations should be recalled in this regard.²⁵ By feeding 60 mgm testosterone propionate to a hypogonad patient daily, they recovered in the urine androgen titers far higher than normal men ever show—yet with *little or no clinical effect on their patient*.

So for the present, at least, we plan to continue our present relatively low doses because of the great expense of the hormones and because,

*These assays were made by the ketosteroid laboratory of the Brady Urological Institute.

from the subjective standpoint, at least, we have felt our treatment to have been adequate

THE FATE OF ANDROGENS IN THE BODY

We make brief mention of what is known of the fate in the body of administered androgens. As previously pointed out, one of the difficulties of androgen therapy has been the rapid destruction or inactivation of the material *in vivo*. The bulk of indirect evidence to date points to the liver as the site of this inactivation.²⁶

Whether subcutaneously or cutaneously administered androgens enter the general circulation via the veins or the lymphatics is as yet unknown, so far as I am aware. It has been definitely shown, however, that pellets implanted in the spleen²⁶ are far less effective than those placed in areas in which the venous return does *not* go by way of the portal system to the liver. This bit of evidence would favor the hypothesis that absorption is via the veins.

Testosterone itself has never been isolated from the urine. Koch² and others have found that the androgenic activity of normal male urine resides largely in the form of androsterone and dehydroiso-androsterone, usually in roughly equal amounts by weight, almost all in the conjugated state, presumably salts of glycuronic acid.

The same authors found that when testosterone propionate was administered to hypogonad patients, the urinary bioassays of these patients were increased in such a degree that if they were in the form of equal parts of androsterone and dehydroiso-androsterone as in the normal, then approximately one-half the injected testosterone could be accounted for in the urine.²⁴ This ratio did not hold, however, for their one patient whose hypogonadism was primarily pituitary in origin, in whose urine far less than 50 per cent of injected testosterone could be accounted for.

Using 17-ketosteroid assays (which usually, but by no means invariably, run roughly parallel to the biological assays) of the urine of our patients on pellet therapy, we have also been able to account for approximately one-half the absorbed testosterone when calculated as milligrams of 17-ketosteroid excreted. On the other hand, only negligible increases of 17-ketosteroids have appeared in the urine when 25 and 50 mgm of methyl testosterone have been given daily by mouth.

OTHER USES OF THE DRUG

The primary importance of any glandular hormone is obviously to replace a deficiency within the organism. But often we find glandular products useful in cases where no deficiency exists for their side effects or therapeutic purposes other than replacement, for example, the many uses to which adrenalin, insulin and thyroid extracts are put every day.

In Cushing's syndrome, Albright²⁷ has found a great increase in protein catabolism, and because of the known nitrogen retaining and tissue building properties of testosterone, has administered the drug to patients suffering with this disease. The results thus far have been surprisingly good from the patients' standpoint, with great increases in strength, lessening of fatigue and the resumption of normal utilization of nitrogenous foods. As might be expected, in some instances in females the clitoris has become enlarged, the beard increased, the voice deepened—but on the whole beneficial effects have seemed to far outweigh the detrimental.

Because of these nitrogen retaining, tissue building or "growth hormone-like" effects, we were tempted to give testosterone to male ateliotic (or symmetrical) dwarfs to observe its effects. Thus far it has been practical to do this in only one patient. One would hesitate to develop sexual maturation in a person to whom adult sexual appetites might prove more of a source of sorrow than otherwise. Just such a patient, however, begged us to accept him as a test object for this specific experiment. Methyl testosterone, for various reasons, was chosen in his case, and 25 mgm has been taken orally per day for eight months. The result has been quite spectacular, in addition to rapid development of adult sexual attributes, this twenty-three year old dwarf has gained twenty-eight pounds, from seventy-two to one hundred pounds, has grown in height two inches, and his span has increased three inches.

Should one use the drug in cases of delayed puberty? Early in our experience we were hesitant to do so, first because of the pituitary tamponade effect with the possibility that sterility might result, and, second, for fear it might make the interstitial cells of the testes permanently "lazy" by taking over their function. But with more experience we now have no hesitation in using the drug in small doses (approximately one-half to two-thirds of that which would bring about primary pattern of response in adult hypogonad patients) in boys who

develop late In every instance thus far we have found that on cessation of the drug puberty continued right along under its own stimulus Webster's experience has been similar in this regard²⁸ Had adolescence not further progressed after stopping the drug, it is likely that puberty would not have occurred at all and, therefore, the replacement would have had to be given eventually anyhow It is not our purpose here to discuss the merits of using APL* or some similar stimulant instead of replacement gonadal hormone, our recent inclination has, however, been to favor the use of testosterone in these cases

EFFECT ON GONADS

In many of our hypogonad patients, the testes, though quite small, have seemed of normal consistency on palpation, and hence we assumed that the difficulty was not primarily testicular (It should be mentioned here, however, that nearly all of the first twenty of our hypogonad cases had been given trial with APL with little or no response) In one or two instances, after *androgenic* therapy, measurements showed slight increases in testicular dimensions, but on the whole, we were able to detect no significant changes, as might be expected In animals, removal of the hypophysis results in rapid degeneration of the spermatogenic elements, but if androgens are administered soon after hypophysectomy in certain animals, spermatogenic function is retained^{29, 30, 31, 32} In young animals, massive doses of androgens have been found to cause atrophy of the testes and permanent sterility,³³ probably by the pituitary depressant effect In our patients, with our relatively much smaller dosage, no such effects have been observed In fact, the experience of one patient is in quite the opposite direction He was a moderately hypogonad man of thirty-two, with small phallus, scant pubescence, no beard and juvenile voice He had been married eight years, no pregnancies having occurred Prostatic secretion was negligible and in several massage specimens only a rare non-motile sperm was found (unfortunately, no ejaculate was studied prior to treatment) Since testosterone therapy was begun three years ago, two pregnancies have occurred, one resulting in miscarriage, the other in a normal child Specimens of ejaculate now show normal sperm counts We believe this to be an extremely important observation because one deduces that in these dosages it need not be feared that administration of testosterone

* Anterior pituitary like substance derived from the urine of pregnant women

will cause sterility. Contrariwise, however, I do not believe that this experience should be used to advocate its indiscriminate use in sterility. This patient must be one in a very small percentage of sterile cases where the subnormal amount of available androgens was still able to maintain spermatogenic faculties, the additional androgens given then allowing increased spermatogenesis. This patient was the only one thus far in our series of forty-six cases in whom we have found any spermatozoa at any time.

In one of our earlier experiences with testosterone, the drug was given to a three year old boy, for other reasons, in doses of 30 mgm twice per week.⁵ Very marked advancement in bone age over a few months prompted us to study this phenomenon in our adult hypogonad patients. In nearly all patients, therefore, we have taken periodic x-rays, but to our surprise, found surprisingly *slow* advancement of their epiphyseal union, though in every instance followed over one year there has been some change.

Before closing I want to touch on one or two other uses for testosterone that have been suggested. With its use in prostatic hypertrophy we have personally had no experience whatever. From the reports that have come to our attention so far, the evidence seems so conflicting that we are dubious whether the administration of androgens alone will remove the necessity for operations in patients with prostatic hypertrophy.

Reports thus far on the use of testosterone in elderly men with so-called menopausal symptoms and depressions are also very confusing. Tangible evidence of cause and effect is uniformly lacking in the reports thus far, and this tends to leave one somewhat skeptical. However, certain experiences of our own have prompted us to feel that the matter deserves further study. A man of considerable prominence in public life, aged over seventy, received 25 mgm testosterone propionate twice a week with great invigorating effect and some gain in weight, and he was altogether enthusiastic. Without the patient's knowledge, we substituted plain sesame oil ampoules (we labeled them plainly as containing the usual amount of testosterone) and the patient promptly returned to his pretreatment level. On resumption of the drug, the same subjective improvement occurred. In this, as well as in several other instances of this type, subjective benefit has been obtained without any manifestation of stimulation in the sexual sphere whatever. In other in-

stances in elderly males, however, we have noted marked sexual stimulation promptly, though the character of the drug was totally unknown to the patient. This whole subject, i.e., the use of androgens in old men, to our mind needs much more study.

For the impotent male, other than those whose condition is specifically lack of androgens, this type of therapy is utterly useless, as might be expected. Likewise, in our hands, no benefit has been derived when testosterone propionate is given to homosexuals in doses larger than those required to bring about our primary pattern of response in hypogonad patients.³

Gynecologists have recently been using testosterone and derivatives in certain types of ovarian dysfunction, with good results reported.³¹ We have no personal experience with androgens in this type of case, and hazard the guess that the use of testosterone will be superseded by other substances when our knowledge of female steroid physiology is further clarified.

Such disjointed facts, ideas and suggestions as I have presented here are in no way presumed to have covered the field suggested in the title. Nor are these remarks intended to have laid down any set rules on such matters as whom to treat, how often, with what dosage or by what method. The whole subject is far too young for anyone, in my opinion, to do this at this time. These remarks have simply been the expression of some of my own opinions on a subject still far from well understood, gained from the experimental facts at hand and the clinical observations so far available. The theoretical material offered to you here may all have to be completely revised on the basis of yet unknown facts.

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SOME ASPECTS OF THE COMMON CONTAGIOUS DISEASES*

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EIGHT million each year is a reasoned estimate of the number of cases that actually occur in the United States of the eight diseases—measles and rubella, chickenpox and smallpox, diphtheria and scarlet fever, mumps and whooping cough. Only a million and a half of these are reported, but the average twenty-year-old American has had slightly more than three of these infections, or one each year for every six children, and there are 48 million children under the age of twenty-one in the United States. Hence these common contagious diseases are of great importance from the viewpoint of frequency of occurrence and loss of time, as well as because of crippling and death. In the last four years the reported death toll from these eight diseases has averaged a total of 11,600 a year. It is impossible to estimate how many people have been crippled in vision, hearing, or other functions by an attack of one or another of these infections or by complications thereof. Hence, the prevention, the diagnosis, and the treatment of these diseases will comprise the scope of this paper. In the time allowed one can stress only the less familiar and the more controversial aspects.

Prevention Of these eight infectious diseases, three are caused by bacteria, and the other five presumably by viruses. Of the bacterial diseases—diphtheria, scarlet fever, and whooping cough—active immunization is obtainable by the use of vaccines in all three diseases. For diphtheria it is universally advocated and a modified toxin is used. For scarlet fever it is widely advocated in theory, but for certain types of people only, and not as a routine public health procedure and an unmodified toxin can be used. For whooping cough it is not yet advocated by public health authorities, but many practicing doctors advise it espe-

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cially for infants, and bacterial protein extracts are used. There is now much evidence to show that the Sauer pertussis vaccine is worth while, perhaps the most convincing of recent results being that of Garvan, who compared the incidence of whooping cough the last four years in Cleveland, where only about 10 per cent of the children have received the Sauer vaccine, with the incidence of the disease in the neighboring Shaker Heights, where possibly 75 per cent have been inoculated with this material. Use of the vaccine was started in 1934. In the four years beginning 1936, the yearly average of whooping cough in Shaker Heights showed a decrease of roughly 83 per cent (83.4) from the preceding seven year period, while the corresponding decrease in Cleveland was but 11 (10.7) per cent. In other words, where the majority of the children had received the vaccine, whooping cough showed a more than proportional decrease. Even when vaccine fails to protect, Kendrick and others have shown that pertussis attacks occurring in vaccinated children are definitely less severe than those in control groups. The vaccine can now be obtained in strengths of 15 and 20 billion bacteria per cubic centimeter, and the total dosage should reach 100 billion. After this has been given, preferably at five months of age, some advocate a small "refresher" injection of 1 cc each year through early childhood.

At the present time it is quite universally taken for granted that all children should be immunized against diphtheria, but attention should be called also to the need for protection of adults. In the last decade and a half since Zingher published statistics about diphtheria immunity as shown by the Schick test, including the finding that 80 per cent of young adults were immune, there has been a distinct decrease of this accidental active immunity presumably due to the lessened likelihood of inoculation by exposure, and this year Thelander reported only 40 per cent of young adults as being immune. Correspondingly, there has been an increase in the proportion of cases of diphtheria that occur in persons twenty years old or over, so that in the last five years in New York City, one-fifth of the cases have been in adults, with a mortality of 42 per cent. Certain types of men, particularly the homeless derelict, are apt not to receive adequate treatment in the first few days of their diphtheria, and the mortality for such cases is very high, 50 per cent in one small series of six.

Two properly given injections of alum-precipitated toxoid at in-

tervals of a month apparently have as high an immunizing power as three injections of plain toxoid, but inasmuch as the alum-precipitated toxoid exists in suspension and requires a larger caliber needle and special care for proper injection, the plain toxoid is probably the more satisfactory preparation for the average practitioner's use. The dosage under six years of age is 0.5 cc for the first injection and then 1.0 cc for the other two at intervals of three or four weeks, while after that age the first dose should be only 0.25 cc. For children who receive this immunization in the first year or two of life, a further small injection of 0.1 or 0.2 cc of toxoid is advocated at the time of entering school at six years of age by the New York City Department of Health.

Schick tests done in the presence of some other acute disease than diphtheria, such as in patients suffering from pneumonia, measles, or poliomyelitis, may give a bullous reaction which Fischer and his co-workers have recently shown does not necessarily mean susceptibility to diphtheria. In some cases a repetition of the Schick test after the patient has recovered from his acute infection has given negative results. Apparently bullous Schick tests are not found in normal healthy children. Incidentally, the Schick relapse rate is "three times higher in children who have had diphtheria than in children who have been actively immunized."

For scarlet fever a properly performed and accurately judged Dick test is evidence of immunity when negative. Klein's work on the immunization of affiliated nurses at the Willard Parker Hospital has been most illuminating on this point. Prior to coming to the hospital for their three months' course of training in the care of contagious diseases, the nurses are supposed to have negative Dick tests, but up to January, 1937, 29 per cent of over a thousand of these nurses contracted scarlet fever during their stay. The hospital thereafter undertook to Dick test each nurse on arrival, and since then no case of scarlet fever has occurred among 1348 nurses known to be Dick negative. During this period eleven cases have occurred among nurses and interns who were not Dick negative.

In general, because of the prevailing mildness of scarlet fever, because of the large amount of toxin necessary to get a durable immunity, and because of the frequency of unpleasant reactions to the injections, immunization with scarlet fever toxin is not usually recommended for all children, but rather for children in such institutions as orphan asy-

lums where scarlet fever occurs frequently, also for members of a family where there is scarlet fever, and for doctors and nurses in positions of special exposure

Passive immunization by means of the administration of serum is well-established for two of these three bacterial diseases, diphtheria and scarlet fever, and as for the third, whooping cough, Bradford, McGuinness and their co-workers have recently stated that convalescent blood serum in doses of 10 to 20 cc, when injected into exposed infants, confers a certain degree of protection for a limited period of possibly three weeks, as does also hyperimmune serum. This protection is particularly important since infants up to five months of age do not respond well to active immunization procedures, nor do young infants inherit an immunity to whooping cough. In fact, at the present time this disease kills more babies than diphtheria, scarlet fever, and measles combined, and the newly established protective value of immune serum is of great importance.

The other five of these contagious diseases, to wit, measles, rubella, chickenpox, smallpox, and mumps, are all presumably due to infection with specific viruses, and as such have several factors in common.

Factor I virus diseases in man are for the most part more easily communicable than the bacterial diseases, of the latter whooping cough being a notable exception.

Factor II viruses cause diseases which as a rule are followed by a lasting immunity, the immunity probably being both cellular and humoral. Herpes of the lips and influenza are probably notable exceptions to this. The late Hans Zinsser has noted that in some of the virus diseases, especially measles and poliomyelitis, the initial immunity may perhaps be constantly reinforced by successive exposures.

Factor III as to chemotherapy, according to Carey and others, there is sufficient evidence to conclude that no sulfonamide compound has yet been found which has any effect on infections caused by a filterable virus.

Factor IV passive immunization with serum might be expected to have some value in those virus diseases in which the virus is generally distributed by the circulation. This has been proved to be the case in measles and apparently also in mumps, but not yet in chickenpox and smallpox, although both are quite certainly also infections in which the virus circulates in the blood. On the other hand, to quote Zinsser again,

one cannot expect much prophylactic value in infections such as rabies, encephalitic processes, and poliomyelitis in which the virus travels centripetally along nerve trunks. Virus infections being intracellular processes, serum injection after the virus has penetrated into susceptible cells, has not proven of preventive or therapeutic value.

Factor V active immunization against these and other virus diseases of man has not as yet been obtained by vaccination with dead or inactive material. Zinsser called this a field still in its infancy. It is of course well known that the virus used for vaccination against smallpox for the past century and a half is an active one modified by passage through calves or, more recently, through chick embryo tissue.

Following such vaccination, no matter how carried out, the virus of vaccinia is distributed generally throughout the body, going from the site of vaccination to the nearer lymph nodes, whence it enters the circulation. Ordinarily it does not produce any lesions in the tissues nor any symptoms except fever and usually some inflammation of the regional lymph nodes. In exceptional cases the virus can cause an encephalitis with tissue change and corresponding symptoms. The secretions of the nasopharynx have been shown to contain virus on the fourth and fifth days after vaccination, therefore, a recently vaccinated person by mere exposure can conceivably cross-infect with vaccinia a susceptible person, and by skin to skin contact can certainly infect such unusually susceptible individuals as children with chronic skin diseases. Even in normal individuals, a routine vaccination may result in a generalized vaccinia but where there is a preexisting skin trouble, as in eczematous babies, vaccination, intentionally or accidentally accomplished, may cause an unusually dangerous condition known as eczema vaccinata, frequently terminating fatally. It is well, therefore, not only to postpone vaccinating children with chronic skin diseases until the eruption has been thoroughly cured, but it is further highly desirable to isolate eczematous children from recently vaccinated persons.

Before leaving the subject of immunization, mention will be made of two research activities that promise further advances in the prevention of disease. First, Rake and Shaffer, Stokes and O'Neil have recently produced a measles vaccine that is prepared by growing the virus on the chorioallantoic membrane of a developing chick embryo, apparently thereby modifying its virulence for mankind. Experimental inoculation of children with this vaccine produced little or no illness but at

the same time stimulated the production of at least partial protection against the unmodified virus. This work is of great promise.

Second, last June at the convention of the American Medical Association, Gladys Dick described a preparation of scarlatinal toxin that could be given in pill form by mouth for immunization. At the present time the material is available for research purposes only.

Diagnosis The etiological and clinical manifestations of these infections are all so well-known that at this time it would seem well to call attention only to a few points of special concern. Cases of measles can be expected in great number in New York City at least this coming winter and spring. In large cities it is a disease usually marked by biennial epidemics, with occasional breakstep years in which an epidemic occurs on a second successive year. New York City has just experienced the other type of breakstep year, the last two springs having been unusually free from the disease. A new generation of little children is with us, and New York must expect perhaps 40,000 cases before July.

Unlike scarlet fever, measles is not spread by its complications, and it need not be isolated after five days from the appearance of the rash. The blood of a person incubating measles, if used for transfusion, can transmit the disease to the recipient at least during the latter half of the incubation period, perhaps even earlier. It is to be hoped that none of the hundreds of people who are donating blood plasma to be sent to England is incubating that disease. The usual sterility tests do not guard against that, at present, remote possibility. However, in *pooled* plasma there are probably enough antibodies to neutralize any possible virus present in a single blood.

In little children measles is frequently confused with rubella and with roseola infantum. The probability in uncertain cases is in favor of a diagnosis of roseola. It should be remembered that rubella (often popularly called German measles) is rare except in the presence of an epidemic, and isolated cases, particularly in little children, are quite uncommon. On the other hand, roseola infantum almost always occurs in two- and three-year olds. Its manifestations are characterized by about three days of unexplainable fever after which there is usually a fairly rapid return of the temperature to normal, followed by the development of a morbilliform or measles-like eruption, which appears first on the body and sometimes spreads to the extremities and the sides of the face. There are no Koplik spots and no appreciable conjunctivitis,

coryza, or cough. The rash lasts only a day or two, and is not followed by pigmentation. The blood shows a decrease in the number of granulocytes. Except for its preliminary fever, the disease is very much like modified measles. However, it is not a result of exposure to measles, and usually occurs in sporadic cases without known causative or subsequent cases.

About chickenpox, several instances have been noted recently in which a case of herpes zoster has been followed 14 to 16 days later by one or more cases of typical chickenpox. It is very unusual, however, to see the reverse, that is, herpes zoster follow a case of chickenpox. A connection between these diseases has long been suspected, but the etiological relationship is still unproved.

For a rapid diagnosis of diphtheria there has been quite a little in the literature about the use of a 2 per cent aqueous solution of potassium tellurite. The liquid is used for swabbing suspicious exudates, and in 15 to 30 minutes a black discoloration of the false membrane and the appearance of the odor of garlic are said to indicate a diphtheritic process. However, false positives appear on any tongue and occasionally in non-diphtheritic lesions, so that any positive test requires bacteriological or clinical confirmation. A negative test suggests but does not prove the absence of diphtheria bacilli. In general the tellurite test is hardly worth doing.

A further point in the differential diagnosis of diphtheria may be mentioned. Diphtheria does not cause erosion or ulceration, but rather a piling up of necrotic confluent material on an inflamed surface. When erosion can be detected, one should suspect syphilis, if the lesion is comparatively painless, or, if painful, an angina due to the Vincent microorganisms, and if the ulcerative pharyngitis is accompanied by much prostration, agranulocytosis should be suspected.

For the diagnosis of diphtheritic myocardial involvement and its after care, the electrocardiogram is of great value. Besides at times revealing delay in conduction time, an entity usually accompanied by such other clinical manifestations of toxicity that an electrical recording is not necessary for diagnosing heart trouble, the electrocardiogram may reveal only an inversion of the T wave. Burkhardt has shown that this is enough indication for keeping a diphtheria patient in bed until the abnormality in the tracing has cleared up, sometimes as long as two months. A diphtheritic myocarditis that does not terminate fatally, does

not result in a crippled heart, however, but goes on to eventual complete recovery

Mumps is a far more important disease from the public health and military standpoints than is generally understood. Throughout the United States Army in the World War one out of every twenty white men and one out of every six colored men had an attack of the disease, and in four camps, all in the far South, over 20 per cent of the soldiers at one time or another during their stay at the camp had mumps. Haven Emerson has stated that in terms of sick wastage and measured by the number of days lost from military service on account of sickness, mumps was the most important disease in the American Expeditionary Force, and Parran has added that next to the venereal diseases, mumps is the most disabling of the acute infections among the recruits. It is my belief that neither authority considered the respiratory infections for which five times as many soldiers were hospitalized as for mumps. Even so, the army lost 3,884,147 hospital days because of this disease, a number exceeded only slightly by that of the days lost due to gonorrhea. Apparently the portal of entry for the specific filterable virus of mumps is by the nose and throat, following which there is a general infection, probably of the blood stream rather than a strictly localized disease. According to Gordon, following the general infection the virus maintains a marked predilection for glandular structure, of which the parotid glands are most often the first affected. However, the other manifestations of mumps, such as orchitis, pancreatitis, and encephalitis, may occur as independent processes preceding involvement of the salivary glands, accompanying it, following it, or occurring without such involvement, and these manifestations should be considered part of the disease rather than complications.

Those lesions which are accompanied by pressure, such as orchitis hemmed in by the tunica albuginea, and encephalitis hemmed in by the cranium, are associated with the most fever, and also are most definitely helped by the relief of pressure. Wesselhoeft strongly advocates early incision of the tunica albuginea in marked cases of orchitis to relieve the intense pain, to shorten the duration of the swelling, and to diminish the extent of atrophy. Incidentally, sterility from mumps is exceedingly rare because only a small proportion of cases of orchitis are bilateral, 16 per cent according to one estimate, and even then it is rare for both glands to lose all function.

Encephalitis is probably far more common in mumps than has been suspected before the last year or two. It may be latent, consisting only of an infiltration of lymphocytes into the spinal fluid, as disclosed by a lumbar puncture, without any clinical manifestations whatsoever to suggest the encephalitis. On the other hand, there may be mild evidences of headache and stiff neck or more definite manifestations of meningeal involvement, with or without those indicating an encephalitis. Serious cases are quite exceptional. The usual duration of symptoms and signs of a mumps encephalitis is not more than three or four days and sequelae are quite rare. Incidentally, the encephalitides following which such sequelae as character change are most common, are the epidemic type, those complicating measles and whooping cough, and that due to lead poisoning.

Treatment In presenting a discussion of advances that have been made in recent years in the treatment of various of these contagious diseases, one must first mention the difficulties involved in evaluating any new therapeutic remedy or procedure. Most of these diseases are so variable in their clinical manifestations and courses, not only from year to year but from case to case, that unless a remedy is tried on a large series of patients during a number of different years, the results being compared with a similar series of coincident control cases, one can only conjecture whether the remedy is beneficial or not.

Many factors can contribute to the cure of the patient besides a particular drug or serum. The violence of an epidemic, the kind of weather at the time of the epidemic, the coincidence of other infections particularly upper respiratory infections, the hospital facilities available and particularly the possibilities of adequate individual isolation, and the skillfulness of medical and nursing attention generally, all provide factors of variability. For instance, in the last ten years at the Willard Parker Hospital the actual methods of treating whooping cough have varied little if at all from year to year. Yet in this decade the annual mortality of whooping cough patients at the hospital has ranged from 8.8 per cent in 1931 to 2.1 per cent in 1939, a variation of over four to one.

As to the management of contagious diseases, in recent years it has become almost universal in hospitals specializing in these maladies to apply individual isolation to each case of each disease. It has been shown that by protecting patients from the illnesses and complications

which others may be suffering in the same hospital or the same ward, cross infections with second diseases may be cut down, complications due to secondary infections may be diminished, and the average length of stay in the hospital may be shortened. On the other hand, when there is overcrowding and a shortage of nurses, as was the case at the Willard Parker Hospital last spring, when with a capacity of 420 patients there was an average of over 500 for about two months, then isolation technique must be given up and there is certain to be, and in this instance there was, an increase in cross infections and in complications.

Isolation technique is founded on the theory that infection is not air-borne, other than by cough droplets, and then only for perhaps five feet. But it has been shown by several workers in England that streptococci can be isolated from the dust of a room 24 hours after a patient has been removed from that room, and it is quite generally believed that both chickenpox and smallpox may be definitely air-borne, perhaps also measles and whooping cough.

Nevertheless, aseptic technique, founded on the principle that contagion is spread by direct or indirect contact only, remains the chief means by which hospital cross-infections can be restricted. Much work has been done by several groups of investigators, such as McKhann, Steeger, and Long at the Children's Hospital in Boston, on the use of the ultraviolet ray in the control of hospital infections, with very encouraging results. The injection of parental blood serum into every child on admission into a general pediatric ward has been advocated by Bar-enberg and his co-workers while Fischer and Raue have similarly used placental extracts. It is known that pooled placental extracts will neutralize diphtheria toxin and poliomyelitis virus, will blanch scarlet fever rashes and protect against measles, and adult sera, particularly if pooled, will probably do as much. However, chickenpox continues to be the bane of crowded hospitals. Although almost never a menace to life in itself, it can prove a dangerously complicating factor when there is sepsis or marasmus, and there is no preventive for this extremely contagious disease.

Chickenpox is now usually treated with special emphasis on cleanliness. Patients are given careful daily baths without rubbing, and are blotted with towels rather than wiped, so as not to break the blebs of the young lesions. Any irritation of the skin is carefully avoided, and from any patient with chickenpox, plaster casts and adhesive plaster

should be removed promptly so as to avoid pressure on the skin and possible gangrenous areas or confluent eruptions

Of the other exanthemata, scarlet fever is particularly variable so that any therapeutic agent is difficult to evaluate. Whereas in recent years virulent forms of the disease are said to have occurred in the Balkans, with a mortality of 10 to 25 per cent, over seven hundred cases of this malady were discharged in 1940 from the Willard Parker Hospital before a patient died there of scarlet fever, and for the past several years in New York City the mortality for this disease has been but a small fraction of one per cent. Two valuable therapeutic sera are at our disposal for the treatment of toxic cases. Human convalescent serum given intravenously in doses of 40 to 100 cc is remarkably effective in neutralizing the toxic manifestations of the disease within 24 to 48 hours' time, and practically invariably without unpleasant reactions. Of horse sera, two manufacturers have recently made preparations of such refinement that the incidence of serum reactions following their administration has been cut well below 10 per cent. Therapeutic results are comparable to those obtained with human serum, and the cost is very much lower. While chemotherapy has as yet proved of little if any value in the treatment of scarlet fever itself, the administration of sulfanilamide during the acute stages has in some series seemed to lessen materially the incidence of complications, but this result has not been obtained universally.

The work of Allison and Brown in England has shown that when cases of scarlet fever are exposed to each other, the patients are apt to infect each other with additional strains of the scarlatinal streptococcus, and most of the complications that occur in the third week or later are due to these cross infections. This may explain why sulfanilamide, which has no apparent effect against the streptococcus of scarlet fever, may in some instances fail to prevent complications, while in other situations, perhaps where the secondary invaders are other microorganisms, it may prove quite protective or therapeutically beneficial.

In the treatment of measles there have been interesting developments. Kohn and his associates have given large doses of convalescent serum, 40 to 50 cc, intravenously, to patients developing measles but still in the preruptive stage, and have apparently materially lessened the severity of the period of eruption. This may prove of considerable importance for patients already suffering from some such condition as pneumonia,

when the complication of an oncoming measles is discovered. This use of serum is the only instance in the virus diseases of man wherein a therapeutic serum, administered after the onset of evidences of the virus infection, is of any apparent value. Even so, in these measles cases the serum must be given at least 24 hours before the appearance of the rash to accomplish even partial modification of the oncoming disease.

As sometimes is the case in scarlet fever, measles patients frequently may be protected from the complications due to secondary infections with streptococci by the administration of sulfanilamide, a procedure which may prove useful in hospital services, but which probably will not become generally used in private practice because of the very low incidence of complications of measles in private homes, particularly of the better class. The pneumonias which complicate measles have proved in a large percentage of cases to be responsive to chemotherapy. Most of these pneumonias are due either to streptococci or pneumococci or to mixed infections. In some, the causative factor is thought to be some kind of filterable virus because, among other reasons, pneumonias are occasionally found complicating measles in which no pneumococci can be found nor a predominating number of streptococci, and for which the sulfonamides do not appear to be beneficial.

Whooping cough pneumonias are given such specific treatment as is indicated from the results of the cultures. Pneumococci are frequently found, and specific serotherapy together with sulfapyridine is helpful for these cases. However, many of the pneumonias in whooping cough are due to the pertussis bacilli themselves, perhaps others to filterable viruses, and in general chemotherapy has not proved as efficacious in the pneumonias of whooping cough as in those of measles.

Habel and Lucchesi of Philadelphia have shown that the convulsions of whooping cough which have so frequently proved fatal in infancy, are usually due to an anoxemia of the brain, secondary to the cyanosis caused by the paroxysms and by bronchopneumonia. Treatment with oxygen and transfusions has in their hands materially lowered the mortality following the convulsions of whooping cough.

Various vaccines have been recommended for the treatment of early whooping cough cases. The detoxified pertussis antigen in five to six doses given one a day or on alternate days, has seemed to mitigate the ensuing disease in some series, but not in others. As to the Krueger undenatured bacterial antigen, Stallings of California has summarized a

number of reports to indicate that daily injections, repeated over 10 to 14 days, have apparently brought considerable relief from troublesome paroxysms for many hours following each dose, but actual curative effects from the use of this vaccine are doubted by many, and the procedure is both expensive and disturbing to the patient

As to diphtheria, the mainstay of treatment continues to be the early administration of adequate doses of diphtheria antitoxin. An injection of not less than 10,000 units intramuscularly is given for the mildest cases, and it is believed at Willard Parker that doses larger than 25,000 units intravenously and 25,000 units intramuscularly are never necessary. Other hospitals, particularly abroad, report that they occasionally give over 100,000 units to some patients.

Following the work of Schwentker and Noel at Johns Hopkins, toxic cases of diphtheria are usually given intravenously considerable quantities of 5 or 10 per cent solutions of glucose. The liver's ability to store glycogen is materially damaged by diphtheria toxin, and glucose by vein has seemed of marked benefit in clearing up the toxic manifestations. Cases of laryngeal diphtheria are usually treated so successfully by aspiration that intubation for diphtheria is now a comparative rarity. Diphtheria itself is becoming an uncommon disease, and for many months this past winter there were admitted to the diphtheria service more patients suffering from streptococcus or staphylococcus laryngo-tracheobronchitis than from diphtheria.

The treatment of these non-diphtheritic laryngeal cases has changed somewhat in the past several months. It was formerly believed that in the presence of a severe streptococcus infection, operative interference with aspiration, intubation, or tracheotomy was contraindicated because there was little or no exudate to remove by suction, but on the other hand there was extensive inflammation, edema, and swelling of the mucous membranes which were aggravated by any mechanical interference. In the past year or two a number of these severe cases have been treated in comparatively early stages with tracheotomy as the only surgical procedure, and something over 70 per cent of the cases severe enough to require an operation have been saved.

Serum reactions are less common than they formerly were, due to the more refined methods of preparing serum. As yet there has been comparatively little experience with the prevention and treatment of these reactions by the use of histaminase. At The New York Academy

of Medicine on April 16, last, Grace Roth from the Mayo Clinic reported confirmation of the work of Foshey and Hagebusch, which showed that five-unit enteric-coated tablets of histaminase, when given by mouth, tend both to prevent and to mitigate serum reactions. Further confirmation is not yet available.

Some doctors believe that if a person is markedly sensitive to horse serum, as shown by positive intradermal and eye tests, he cannot safely be given therapeutic doses of serum. The case is probably very rare indeed to which serum cannot be administered if proper precautions are taken. An unemployed negro longshoreman was recently admitted to the Willard Parker Hospital with an extensive pharyngeal diphtheria of three days' duration. His intradermal and eye tests for serum sensitization were both positive. A tourniquet was placed loosely high around one thigh and 0.1 cc. of serum was injected subcutaneously into the mid-thigh, accompanied by 3 minims of adrenalin. Each half hour a larger dose was given until at the end of nine doses a total of 35,000 units had been administered, part subcutaneously and part intramuscularly, each injection being accompanied by the administration of 3 minims of adrenalin, and both legs being eventually used. There was no immediate reaction to the serum, and the following day the diphtheritic process had largely disappeared.

Incidentally, for a patient's comfort, the serum should not be given in the outer or lateral aspect of the thigh, the fascia lata preventing swelling as a result of the injection, and causing the patient undue discomfort. Most patients prefer to receive a large amount of serum in the gluteal muscles.

Before closing I will add a paragraph or two about poliomyelitis. Of new information about the disease there is little that is not negative. While the virus in scattered instances can be found in the secretions of the nose and throat, it is found more commonly in the stools, and in the presence of an epidemic of the disease, it can be identified even in the stools of apparently healthy persons. It has been detected more readily in the stools of cases of the usually unrecognized abortive type than in paralytic patients. Virus can exist in large amounts in sewage in which it can be transmitted at least an eighth of a mile.

As Paul said a week ago in New York,* we do not know how the virus enters the body, nor how to prevent its entering. Because the nasal

* Paul, J. R. Poliomyelitis. *Bull. New York Acad. Med.* 1941, 17, 259.

bulbs are so seldom involved, more and more students of the disease are coming to believe that a nasopharyngeal portal of entry is unusual rather than the rule, and that the disease is perhaps transmitted by a number of channels, as by direct contact with an infected person or by such other means as infected food or water. Paul mentioned the possibility that there may be other than human hosts or reservoirs.

Thus, there is little new to recommend for the prevention of the disease. In epidemic times, personal hygiene should be stressed as well as the avoidance of excessive fatigue and of unnecessary exposure to any illness. Milk should be pasteurized and drinking water boiled. In order to keep water out of the nose, swimming might well be omitted particularly wherever there is a possibility of contamination with sewage. The removal of tonsils and adenoids should be postponed, in fact, any procedure that might traumatize the nasopharynx should be avoided. Psychologically and practically, it is well in any given community that recommended regulations should be made uniform and authoritative by the health officers.

As for treatment, complete rest is almost the whole story. In the presence of an epidemic, any child with only a minor illness such as a slight cold or an alimentary disturbance, should be considered a presumptive abortive or preparalytic case and be given prolonged bed rest with a very minimum of handling. In more definite cases, parents should be made to understand that absolute rest is so vital that even a transfer to a hospital might be harmful, except of course where the use of a respirator is indicated. Many cases might be cited where a patient continued in normal activity with what seemed to be a minor illness, and then developed extensive paralysis. Paul related several of these last week, and we all can remember vivid instances.

When a diagnosis is definite and muscle weakness has appeared, then the patient should be put in a neutral position with no muscles stretched or under tension, and should be protected from all unnecessary handling or other disturbance. At the Willard Parker Hospital no serum is used. If a patient seems toxic or in any way seriously involved, he is given a 10 per cent glucose solution intravenously. This past summer we have experimented with massive doses of thiamin chloride intravenously and in the twelve or fourteen cases in which it was used, have thought we obtained astonishingly rapid recoveries of those muscles which on admission showed only weakness, not complete paralysis.

There were no control cases, so nothing has been proved. However, we shall probably try it another season.

In summary, we have noted how serums are curative for some bacterial diseases, and chemicals are for many. Last spring, at The New York Academy of Medicine, Perrin Long pointed out that about 75 per cent of bacterial infections now respond to chemotherapy, notable exceptions being whooping cough, typhoid fever, tuberculosis, and common colds. It is greatly to be hoped and rather confidently to be expected, that for these remaining bacterial diseases the next few years will see the discovery of specific remedies. The virus diseases of man are still without either a specific curative serum or a therapeutic chemical. Perhaps for these infections also therapeutic agents of great efficiency may be revealed.

THE MARRIAGE OF MEDICINE AND CIVIL GOVERNMENT*

HAVEN EMERSON

It is for me a happy accident of the passing years and of chance circumstance that I have been privileged to attend as member of the official family of our community both the golden, and this, the diamond wedding anniversary of a marriage of medicine and government which has produced enduring values

Among the offspring of this union have been more vigorous and self-perpetuating features of growth and survival over the recent generations than have followed any other event in the social progress of our times

Hardly had the guns and bugles of our Civil War ceased their clamor, and military uniforms been doffed for work-a-day clothes before there cropped up in the large cities of this country a harvest of new ideas and hopes, and a philosophy of social reconstruction worthy of the triumph of the spirit of union across the continent. Men who had experienced the devastations of battle, hunger and pestilence brought home from the army also vivid memories of the beneficent protection carried into bivouacs, hospitals and prison camps by the agents of the United States Sanitary Commission. Our young veterans recognized discipline and authority as indispensable to an effective use of the slender resources of medical science of the day.

It must be recalled that the germ of our own particular sanitary reconstruction had begun to grow before the outbreak of the Civil War. It was in fact on February 3, 1859 that the Senate of the State of New York received the report of its select committee, appointed in April of the previous year to investigate the Health Department of the City of New York.

Three facts were established in this report. The City of New York had a higher ratio of mortality than other large cities in this country and in Europe. The main causes of the excessive mortality were over-

* Delivered March 5, 1941 at the exercises commemorating the 75th Anniversary of the New York City Board of Health, in the Auditorium of the Health Building, Manhattan.

crowded tenement houses, want of practical knowledge of the proper mode of constructing such houses, deficiency of light, imperfect ventilation, impurities in domestic economy, unwholesome food and beverages, want of cleanliness in streets, and at wharves and piers, and finally a general disregard of sanitary precautions, imperfect execution of existing ordinances and a total absence of regularly organized efficient sanitary police. The remedy to be relied upon to bring health to the City was "the establishment of a thoroughly organized medical police, at whose head should be an active and experienced medical man."

The war brought this official effort, intelligent, constructive and promising as it was, to an abrupt end and it was not until 1865 that the even more deplorable state of the population and their housing was again studied with the results we are here assembled to commemorate.

It took but one year of concentrated well directed voluntary study of the prevalence of sickness and death in every block of the city by the physicians of New York to convince the Citizen's Association and the State Legislature that the day of corruption, incompetence and indifference must give way to a pattern of health service consistent with the ambitions and necessities of the nation's metropolis.

In thoroughness and in practical effect the classical Sanitary Survey of New York of 1865 has not been excelled, nor has any agency of public betterment in the past 75 years created as great or as permanent an effect upon the way of life and upon the use of government for social benefit as did the Council on Hygiene and Public Health which organized the study, published the report and made its conclusions effective by supporting the enabling legislation.

The following paragraph from that report reveals the sensitiveness of this body of surveying physicians to the value of voluntary as well as official efforts for the health of the city:

"Earnestly as we would strive to secure the application of adequate laws for the improvement and protection of the public health, we would, with equal earnestness, and for the same ends, urge that individual and organized efforts be put forth, for all these agencies must eventually cooperate in giving to the population of this city that protection to life and health which an enlightened people claim to be due to all classes of society."

It was the legal astuteness and the social statesmanship of a master of sanitary law, Dorman B. Eaton, that made good use of the opportunity

out of which came a body of such broad and adequate powers for public health control that they have needed little if any enlargement and have suffered no limitations since that date

This was no trial marriage but a devoted union for better or worse until death do us part In this spirit the medical sciences joined hands with the elder partner, the city government, with due formality of contract, and the Metropolitan Board of Health was the family name

No well-read New Yorker needs to be reminded of "The City that Was," a political epic, a medical romance, a news thriller of relatively recent years wherein are told those stirring tales of Dr Stephen Smith's success in outwitting landlords and aldermen and driving out of the cellars and cesspits of a dangerously overcrowded population the cruder forms of sanitary abuse Almost unbelievable are the reports of school rooms with one-fourth the space we now think necessary for each child There was the well-supported evidence of the first sanitary chemist, Professor Chandler, that a quarter of the milk sold consisted of more or less polluted tap water and for this water in their milk the people paid about four million dollars a year

Epidemics of Texas fever decimated the cattle yards, the gas nuisance blighted large areas of workmen's homes, the kerosene lamp was a common fire hazard challenging sanitarians as well as underwriters Even churches were so overcrowded as to threaten the health of congregations More than one quarter of the samples of milk tested revealed gross physical and chemical adulteration The ever-recurring threat of poisonous cosmetics, hair tonics and dyes, skin enamels and powders was old and familiar then as now to the health officers of the city Equine influenza periodically swept away its thousands of horses

It was the medical officers of the Health Department whose report upon the working conditions of horse-car drivers revealed with dramatic thoroughness the miserable barbarity of their employment from fifteen to seventeen hours a day on their feet behind the clanging dashboards It was these same inspectors who studied the home and factory conditions of the tobacco industry and came to the conclusion that the home cigar-makers were better paid, had better food and in general lived better lives than was true of factory workers in the same trade

It was the relative infertility among tobacco workers in general which was at that time a cause of more anxiety than any adverse health conditions found among them

Truly the city of that day was a rapacious Moloch devouring the most vigorous and ambitious youth from our own farms and from the shiploads of immigrants. Death rates often exceeded birth rates and it was a very real question whether city life could exist on these terms. It remained to be proved whether such large gatherings of human beings could survive the very conditions upon which the wealth and culture of their days depended.

The answer did not come at once, nor has the challenge of man's arrogance in a metropolitan existence been permanently met in our time.

Even today, at the zenith of our health accomplishment the margin between living and dying is but slender and unstable. With birth rates of thirty-six and death rates of thirty-five per thousand of the population in some of the years of the first decade of the new regime it was difficult to prove the value of protective measures.

Man's struggle for survival has ever depended upon the accumulating treasury of knowledge of human biology of which the medical profession has been the self-perpetuating trustee and practitioner. Only as the facts of causes and effects became obvious were the innumerable handicaps to man's existence reduced by conscious control. Most of the information upon which the triumphs of the latter decades have been based was obscure or wholly lacking when the sanitarians of 1866 attacked the Augean stables that were then our city slums. There was but one certain and specific protection against an ancient and persistent pestilence, vaccination for the smallpox, and quinine and mercury were the only drugs for which true curative properties could be claimed. With the wisdom of a simple faith in communal cleanliness, in a fairer form of municipal housekeeping, the sanitary inspectors and the authors of sanitary ordinances set themselves to create an environment upon which could be built the finer structure of wholesome family life.

From the very beginning of the work of the Metropolitan Board of Health there was provision for fact-finding and original inquiry as the basis for public policy, the chemists first and soon after the microscopists laying the sound foundations for that unique creation within city government, so creditable to New York, the public health laboratory, out of which has grown so glorious an accomplishment and tradition.

With a sure eye for relative values, for the needs of first and urgent importance, the Board of Health established a permanent concern for

three of the standard functions of government health service, the record and analysis of the human family, our vital statistics, control of man's material envelope, or sanitation, and, most urgent at that time, protection against pestilence. These occupied the master rooms in our new house of health.

It was not until after the first quarter-century of growth that the fourth major function, the diagnostic laboratory was added to the enlarged mansion in 1892, to be followed just before the half-century by a spacious wing for childhood and maternity and for the latest member of the family, health education.

Whether or not by *words* exactly suited to our modern conception, the original Metropolitan Board of Health did by their *acts* define public health as the application of the sciences of preventive medicine by government for social ends. These physicians, chemists, engineers and lawyers of 1866 saw clearly the boundary between individual and administrative medicine, and while holding closely to their cooperative dependence upon the family and hospital physician, developed the use of public authority and tax resources for general as distinct from personal benefits. Without meticulous distinction between the curative and preventive resources of medicine they took pains to make their efforts supplementary and accessory to, rather than substitutes for the work of their colleagues of the private office, the public dispensary and the hospital ward.

Within six weeks of the organization of the Metropolitan Board of Health it declared "evidence of great and imminent danger to the public health by reason of impending pestilence" and requested the Governor of the State to extend to it extraordinary powers. Thus a cholera epidemic was for the first time in the city's history met by an informed professional leadership clothed with adequate authority and supplied with sufficient funds.

From that time forward the broad powers granted to the Board of Health by the legislature were tested in a multitude of crises of sanitation, politics and finance. Almost without exception, and certainly without substantial damage to its usefulness, the sanitary code of ordinances enacted by the Board, its enforcement of them and its quasi-judicial hearings on appeal against its orders have been supported and strengthened by the courts.

This Board of Health of the Metropolitan Sanitary District of the

State of New York became an *imperium in imperio* in all matters related in any way to the health of the people of this city, limited only by the proper restraint that its ordinances, and actions based upon them, should be neither arbitrary nor tyrannical. The legal structure was so sound and its support by the courts so general that it has served as a model for many another city and state as the basis for public health statutes and local ordinances. The counties of New York, Kings, Westchester and Richmond, and the towns of Newtown, Flushing and Jamaica, in the county of Queens were included in its jurisdiction.

Lest we indulge in unseemly and parochial self-laudation, it is well to recall that our critical date of 1865 for the Sanitary Survey, which was, let us say, the year of courting and betrothal that brought medicine and government to the desire or necessity of a New York marriage, was but the third in historical sequence, the Sanitary Survey of Massachusetts by Lemuel Shattuck of 1855 and the Sanitary Survey of the Labouring Population of Great Britain by Edwin Chadwick in 1842 having set the stage for the first basic state and national public health laws in the modern manner, as our physician's study did for a city community.

Medicine had its poets then, and sanitation had not gone unsung as these verses of Dr. Holmes bore witness at the meeting of the National Sanitary Association in 1860. Anatomist, surgeon, obstetrician, sanitarian, Oliver Wendell Holmes rang out a prophetic challenge which still awaits its adequate response.

"What makes the Healing Art divine?
The bitter drug we buy and sell,
The brands that scorch, the blades that shine,
The scars we leave, the 'cures' we tell?"

"Are these thy glories, holiest Art,—
The trophies that adorn thee best,—
Or but thy triumph's meanest part,—
Where mortal weakness stands confessed?"

"God lent his creatures light and air
And waters open to the skies,
Man locks him in a stifling lair,
And wonders why his brother dies!"

"In vain our pitying tears are shed,
In vain we rear the sheltering pile
Where Art weeds out from bed to bed
The plagues we planted by the mile'

"Be that the glory of the past,
With these our sacred toils begin,
So flies in tatters from its mast
The yellow flag of sloth and sin

"And lo' the starry folds reveal
The blazoned truth we hold so dear
To guard is better than to heal,—
The shield is nobler than the spear "

When we think of those early pioneers in municipal health administration, the collective bridegroom of the wedding of 1866, and while we still cling to their determination to make practical realities out of the potential blessings of medical science, in spite of the recurrent interruptions of war and its increasing present threat, we can say as Dr Osler did at his farewell dinner in this city

"What the future has in store for me I cannot tell, you cannot tell
Nor do I much care as long as I can carry with me, as I shall, the memory of the past you have given me Nothing can take that away "

Nothing can deprive us, as we move on into the last quarter of our city's first century of health, of the sense of obligation, of the memory of performance, of high resolves, of the salvaging of multitudes which our ancestors of medicine and government achieved way back yonder, those 75 years ago

Let us keep faith with those giants who built the home we occupy in great safety and much comfort, and devote ourselves with equal determination to "the building of a better tabernacle for the soul of man to inhabit," for such we are told by Sir George Newman of the British Ministry of Health is the purpose of preventive medicine

May we say now and pledge our successors to declare that

"We have loved no darkness
Sophisticated no truth
Nursed no delusion
Allowed no fear "

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Leipzig, Thieme, 1940, 286 p
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Ann Arbor, Edwards, 1940, 113 p
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Springfield, Ill., Thomas, 1941, 265 p
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London Secker, 1940, 144 p
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N Y Reinhold, 1941, 1362 p
- Thoma, K H *Oral pathology*
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[Leeds, Jowett], 1940, 63 p
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Oldenburg Stalling, [1941], 193 p
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Wash, U S Public Health Service, 1940, 1 v
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[Carlisle Barracks, Med Field Service School], 1940, 180 p
- Vaughan, W T *Strange malady, the story of allergy*
N Y, Doubleday, 1941, 268 p
- Vernon, H M *The health and efficiency of munition workers*
London, Milford, 1940, 138 p
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- Waite, F C *History of the School of Dentistry of Western Reserve University*
Cleveland, [Western Reserve Univ], 1940, 223 p
- Weinberger, B W *Pierre Fauchard, surgeon-dentist*
Minneapolis, Pierre Fauchard Academy, 1941, 102 p
- Weisman, A I *Spermatozoa and sterility*
N Y, Hoeber, [1941], 314 p
- Werner, B C F *Das Labyrinth*
Leipzig, Thieme, 1940, 400 p
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Springfield, Ill., Thomas, 1941, 459 p
- Williams, J F *Healthful living* 3 ed
N Y, Macmillan, [1941], 600 p
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N Y, Appleton-Century, [1941], 1021 p
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Stuttgart, Marquardt, 1940, 266 p

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 6—*The New York Academy of Medicine* Executive Session—a) Reading of the minutes, b) Action on proposed amendment to Constitution ¶ Scientific Program—Newer Surgery of the Heart and Large Vessels—a) Medical aspects, H M Marvin, Associate Clinical Professor of Medicine, Yale University School of Medicine, b) Surgical aspects, William DeWitt Andrus, Associate Professor of Surgery, Cornell University Medical College ¶ Report on Election of Fellows

FEBRUARY 20—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The fifth Harvey lecture, "The Significance of the Sulfur-Containing Amino Acids in Metabolism," Howard B Lewis, Professor of Biological Chemistry, University of Michigan Medical School

MARCH 6—*The New York Academy of Medicine* Executive session—a) Reading of the minutes ¶ Scientific Program—Current Concepts Regarding Benign Lesions of the Small Intestine—a) Roentgenological aspects, Ross Golden, Professor of Radiology, College of Physicians and Surgeons, Columbia University, b) Surgical aspects, Claude F Dixon, Associate Professor of Surgery, Mayo Foundation, University of Minnesota, c) Medical aspects, Burrill B Crohn, Associate in Medicine, The Mount Sinai Hospital ¶ Report on Election of Fellows and Honorary Fellows

MARCH 20—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The sixth Harvey lecture, "Some Cardiac Effects of the Inhalant Anesthetics and the Sympathomimetic Amines," Walter J Meek, Professor of Physiology, University of Wisconsin

APRIL 3—*The New York Academy of Medi-*

cine Executive Session—a) Reading of the minutes, b) Presentation of Certificates of Fellowship ¶ The Sixteenth Hermann Michael Biggs Memorial Lecture, Clarence A Mills, Professor of Experimental Medicine, University of Cincinnati College of Medicine on "The Relation of Climate and Geography to Health" ¶ Report on Election of Fellows

APRIL 10—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The seventh Harvey lecture, "Hormones and the Process of Aging," Leo Loeb, Emeritus Professor of Pathology, Washington University School of Medicine

SECTION MEETINGS

FEBRUARY 4—*Section of Dermatology and Syphilology* Presentation of cases of syphilis of the skin and mucous membrane, in conjunction with the Health Department program for educating the profession in the diagnosis and treatment of syphilis ¶ Discussion of cases ¶ Executive session

FEBRUARY 7—*Section of Surgery* Reading of the Minutes ¶ Presentation of cases—a) Carcinoma of ampulla of Vater, two years postoperative, John A Imm (by invitation), Discussion, Pierre Renaud (by invitation), b) Stricture of the common bile duct with calculi Symptoms simulating coronary disease Operation—one year follow-up, Kenneth M Lewis, Discussion, Morris K Smith, c) (1) Acute cholecystitis, cholelithiasis in a girl, age 15, (2) Calcium carbonate gall-bladder, Edward D Truesdell ¶ Papers of the evening—a) Obstructive jaundice due to carcinoma of the pancreas The choice of operative procedure, Myron A Sallick, John H Garlock, Discussion, Richard Lewisohn b) The role of the liver in surgery, John H Mulholland, Discussion, Murray MacG

Gardner (by invitation) † General discussion

FEBRUARY 11—*Section of Neurology and Psychiatry* Reading of the minutes † Presentation of case—Parkinson syndrome associated with hemiatrophy of central origin, Orman C Perkins, Max Gold (by invitation), Discussion, Charles A McKendree. † Papers of the evening—a] A consideration of the surgical treatment of craniopharyngiomas, Jefferson Browder, Discussion, Ira Cohen, b] Occlusion of the sagittal sinus, Harold R Merwarth, Discussion, Byron Stookey, J E J King, c] Therapy in Parkinsonism, A critical evaluation, A M Rabiner, Morton Hand (by invitation) † General discussion † Executive session

FEBRUARY 13—*Section of Pediatrics* Reading of the minutes † Papers of the evening—a] Weak feet, weak ligaments, and poor posture, George L Inge, Discussion, Katharine G Dodge b] Joint tuberculosis diagnosis and treatment, Alan deF Smith, Discussion, Mather Cleveland, c] Congenital dislocation of the hip, Beckett Howorth, Discussion, I Campbell Thompson d] Scoliosis, William H von Lackum (by invitation), Discussion, John R Cobb

FEBRUARY 17—*Section of Ophthalmology* † Exhibits 7 00 to 8 30 o'clock—a] Demonstration of fluorescence of lens material and of certain lesions, with long-wave ultraviolet, Elliott B Hague, Buffalo (by invitation), b] Histology studies of grafted eyes and regenerating lenses, L S Stone, New Haven (by invitation), c] Colored photomicrographs of the ocular blood vessels, Robert K Lambert, d] Slit lamp cases, Milton L Berliner, Gordon M Bruce, Girolamo Bonaccolto, Sidney Fox (by invitation) † Executive Session † Presentation of cases—a] Three cases of Kaiser-Fleischer Ring in hepatolenticular degeneration, Samuel Gartner (by invitation) b] Hemangioma of orbit, Donald W Bogart (by invitation) c] Squamous cell carcinoma of cornea, Samuel Evans

(by invitation) † Papers of the evening—a] The anatomy and functional significance of the primary endings of the optic nerve in man and animals (lantern slides), Otto Warburg (by invitation), b] Procedures in intracapsular cataract extraction, Daniel B Kirby, c] Return of vision in the vertebrate eye following repeated transplantations (colored motion picture), L S Stone, New Haven (by invitation), d] special features of the ocular blood vessels, Robert K Lambert

FEBRUARY 18—*Section of Medicine* Reading of the minutes † Papers of the evening—a] Observations on the pathologic physiology of the human pancreas, Louis Bauman, Discussion, Allen O Whipple, b] Paravertebral sympathetic block with alcohol for the relief of cardiac pain, Robert L Levy, Richmond L Moore (by invitation), Discussion, Harold J Stewart, Bronson S Rav † General discussion † Executive session

FEBRUARY 19—*Section of Genito-Urinary Surgery* Reading of the minutes † Papers of the evening—a] Urinary extravasation, Edward O Finestone (by invitation), b] Hemangioma of the urinary bladder, with coincident papillary carcinoma (case report), Joseph A Hyams, c] Lymphosarcoma of the prostate and epididymis (case report), Joseph Ienenbaum, d] Actinomycosis of the kidney (case report), Frederick T Bond (by invitation), e] TriPLICATION of the renal pelvis and ureter on the right side (case report), Stanley R Woodruff, Jersey City † General discussion † Executive session

FEBRUARY 19—*Section of Otolaryngology* Reading of the minutes † Papers of the evening—a] Non-surgical treatments for deafness 1 Psychotherapy, prostigmin, radiotherapy, Edmund P Fowler, Jr 2 Drugs, vitamins, endocrines, prostheses, William A Greenfield (by invitation), b] The consequences of shortened intermaxillary dis-

tance H R Junemann, DDS (by invitation) c] What is being done for deafness of school children, Westley M Hunt, d] Incidence of surgical procedures using acute mastoiditis as an indicator—a study over a period of eleven years with detailed statistics for New York and other geographic sections of the United States, Harold W Corva (by invitation), Discussion, Marvin F Jones, William H Best (by invitation) f General discussion

FEBRUARY 21—*Section of Orthopedic Surgery* Reading of the minutes f Papers of the evening—a] The intermuscular lateral approach for removal of cervical rib Samuel Kleinberg b] Anatomical evaluation of symptoms due to cervical rib, Russel H Patterson c] The scalenus anticus syndrome with and without cervical rib, report of 25 cases, I M Donald (by invitation), Birmingham, Alabama f Discussion, Kristian G Hansson (by invitation), Clement B Masson f General discussion

FEBRUARY 25—*Section of Obstetrics and Gynecology* Executive session—reading of the minutes f Papers of the evening (Program by Bellevue Hospital, Department of Obstetrics and Gynecology), Prevention and treatment of puerperal infection—a] Method of prevention of postpartum infection, George Bowen (by invitation), b] Treatment of group A hemolytic streptococcus infection in the puerperal state, Gerhard Ahnquist (by invitation), c] Severe anaerobic streptococcus septicemia in the puerperium with recovery (a case report), Hiram Salter (by invitation) d] Bacteriological characteristics of anaerobic streptococcus recovered from postpartum patients, Melvin L Stone (by invitation) f Discussion, Thomas Francis, Jr

MARCH 4—*Section of Dermatology and Syphilology* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee f Presentation of cases—a] City Hospital b]

Polyclinic Hospital c] Miscellaneous cases f Discussion of cases

Section of Pediatrics There was no meeting of the Section in March because of (1) the meeting of the American Academy of Pediatrics (Region 1) at New Haven, Conn, on March 27, 28 and 29 and (2) the joint meeting with the Section of Obstetrics and Gynecology and the New York Pathological Society in April, in addition to the regular meeting

Section of Surgery The March meeting of the Section was not held on the regular date. Instead, the Section of Surgery held a combined meeting with the Section of Medicine on March 18 (qv)

MARCH 11—*Combined Meeting Section of Neurology and Psychiatry and the New York Neurological Society* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee f Papers of the evening—a] The effect of liver therapy on the pathways of the spinal cord in subacute combined degeneration, Charles Davison Discussion Lewis D Stevenson, b] The psychopathology of psychopathic personality, George S Sprague Discussion, Karl M Bowman, A A Brill c] Ambulatory schizophrenias, Gregory Zilboorg Discussion, A A Brill f General discussion

MARCH 12—*Section of Historical and Cultural Medicine* Executive session—a] Reading of the minutes, b] Report of Nominating Committee f Paper of the evening—Diseases in the Five Books of Moses, in the light of Egyptian medical papyri, Abraham S E Yehuda f General discussion

MARCH 17—*Section of Ophthalmology* Exhibits—a] Results of treatment of tumors in the region of the eye by irradiation, William Law Watson b] Gross specimens of ocular neoplasms Pathology Department, New York Eye and Ear Infirmary Edgar Burchell (by in

itation), c] Tumors of the eye, lids, and orbit, Pathology Department, Institute of Ophthalmology, Charles A Perera, John S McGavie (by invitation) Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee Memorial to Dr A Edward Davis by Clyde E McDannald ¶ Papers of the evening *Tumors of the Eye and Adnexa*—a] The eyeball, Theodore L Terry, Boston, Mass (by invitation), b] The orbit, C S O'Brien, Iowa City, Iowa (by invitation), c] the lids and conjunctiva, Bernard Samuels, d] Discussion, James Ewing

MARCH 18—*Combined Meeting Sections of Medicine and Surgery* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee for each Section ¶ Papers of the evening—a] The functional evaluation of renal disease in hypertension 1 Bilateral studies, William Goldring, 2 Unilateral studies, Herbert Chasis (by invitation), b] Arterial hypertension—definition of the problem, Henry A Schroeder (by invitation), c] Surgical treatment of hypertension, (presentation of cases), Carnes Weeks, d] Nephrectomy for arterial hypertension, George W Fish, e] Surgical treatment of hypertension, Frank Glenn, f] Splenonephropexy in experimental and human hypertension, David M Weeks, Discussion, Homer F Smith ¶ General discussion

MARCH 19—*Section of Genito-Urinary Surgery* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee ¶ Papers of the evening *Symposium on Postoperative Complications*—a] The cardiac and pulmonary complications of urological surgery, Edwin P Mavnard, Jr, Brooklyn, Discussion opened by William H Iohman, Brooklyn, b] Water balance and shock, Walter G Maddock, University Hospital, Ann Arbor, Michigan (by invitation) Discussion opened by George F Cahill ¶ General discussion

Section of Otolaryngology Instead of the regular meeting of the Section of Otolaryngology at the Academy, the Section held a combined meeting with the Section on Otolaryngology of the College of Physicians of Philadelphia at their building in Philadelphia, March 19 ¶ Papers of the evening—a] Some interrelationships of otolaryngology and hematology, Thomas Fitz-Hugh, Jr, Discussion, Andrew A Eggston, b] Some external nasal deformities and methods used in their repair, Warren B Davis, Discussion, Arthur Palmer, c] Pharmacology and toxicology of the sulfonamide compounds, Harrison F Flippin (by invitation), Discussion Wesley C Bowers Executive session—Appointment of Nominating Committee

MARCH 21—*Section of Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee. ¶ Papers of the evening—a] Acromioclavicular separation New method of repair Illustrated by moving pictures, Boardman M Bosworth, b] Deformities of the femur resulting from arrestment of growth, Edward L Compere, Chicago, Illinois (by invitation), c] Aseptic necrosis and bone drilling, Ernst W Bergmann (by invitation), Discussion, Alan De Forest Smith, Donald E McKenna ¶ General discussion

MARCH 25—*Section of Obstetrics and Gynecology* Executive session—a] Reading of the minutes, b] Appointment of Nominating Committee. ¶ Papers of the evening—a] Fracture of the femoral neck following roentgen therapy for gynecological malignancy, Hyman Strauss (by invitation), Joseph L McGoldrick (by invitation), Discussion, Maurice Lenz, William P Healy, b] The theca-interna cone and the ascensus of the Graafian follicle, Erwin O Strassmann, Houston, Texas (by invitation), Discussion, Alfred Plaut, Herbert Traut, Grete Stohr (by invitation)

APRIL 1—*Section of Dermatology and Syph-*

ology Executive session—Nomination of Section Officers and one member of Advisory Committee ¶Presentation of cases—The Skin and Cancer Unit of Post-Graduate Hospital ¶Discussion of cases

APRIL 4—*Section of Surgery* Executive session—a] Reading of the Minutes, b] Nomination of Section Officers and one Member of Advisory Committee ¶Presentation of cases—a] Aneurysm of splenic artery—removal—recovery, Irwin E. Siris, Discussion, Leo I. Lowe, b] Leiomyosarcoma of the stomach, Edwin B. Leckerson, Discussion, Thomas H. Russell, c] Pyloric obstruction caused by heterotopia of Brunner's glands, James H. Kidder (by invitation), Discussion, Harold B. Keves, d] Non-specific ileitis—resection—apparent cure, Gaston A. Carlucci, Discussion, Lester Breidenbach ¶Papers of the evening—a] Surgical problems in the treatment of gastrojejunal ulcers, Ralph Colp, Discussion, John J. Westermann, Jr., b] Benign tumors of the stomach, Laurence Miscall Discussion, Guilford S. Dudley ¶General discussion

APRIL 8—*Section of Neurology and Psychiatry* Executive session—a] Reading of the minutes b] Nomination of Section Officers and one member of Advisory Committee ¶Presentation of cases—Cerebellar agenesis, Ira Cohen Discussion, H. A. Riley ¶Papers of the evening—a] Peculiarities of the blood plasma in cases of multiple sclerosis, Tracy J. Putnam, William S. Orr (by invitation), Mildred G. Gray Ph.D. (by invitation), b] Fiber dissociation in peripheral neuropathy, Herman Wortis, Martin Stein (by invitation), Norman Jolliffe, Discussion, F. D. Friedman, Louis Hausman ¶General discussion

APRIL 10—*Section of Pediatrics* Executive session—a] Reading of the minutes b] Appointment of Nominating Committee ¶Papers of the evening—a] Behavior disorders associated with intracranial tumors in childhood (case reports), Wil-

liam S. Langford (by invitation), Discussion, Lauretta Bender b] The results of the treatment of infantile hydrocephalus by endoscopic coagulation of the choroid plexuses, Tracy J. Putnam, Discussion, John L. Scarff, c] Acute encephalitis of unknown origin with cerebellar symptoms in children, Walter O. Klingman, Richard G. Hodges (by invitation) Discussion, Peter G. Denker

This Section also held a joint meeting April 22, with the Section on Obstetrics and Gynecology, the New York Pathological Society, and the New York City Committee on Prematurity. See program under Section of Obstetrics and Gynecology.

APRIL 15—*Section of Medicine* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶Papers of the evening—a] Modern clinical evaluation of liver diseases, Franklin M. Hanger, Discussion, Alexander B. Gutman, b] Diabetes and tuberculosis, Herman O. Mosenthal, Morton F. Mark (by invitation), Discussion, Edward Tolstoi ¶General discussion

APRIL 16—*Section of Genito-Urinary Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶Papers of the evening—a] Division of renal isthmus in horseshoe kidney (case report), Robert Gutierrez, b] The management of ureteral calculi, with report of five cases of vaginal uretero lithotomy, Edward W. Campbell, Philadelphia (by invitation) ¶General discussion

APRIL 16—*Section of Otolaryngology* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶Presentation of cases—Paraffinoma of the nose, George D. Wolf ¶Papers of the evening—a] The "Illusion of Loudness" of tinnitus, its etiology, significance and treatment, Ed-

mund Prince Fowler, Discussion, R Lorente de Nó (by invitation), b] Acute infections of the jaws, Francis S McCaffrey, DDS, c] Fractures of the maxillary bones, Douglas B Parker (by invitation), d] Maxillary sinusitis of oral origin, closure of oro-antral openings, Henry S Dunning ¶ General discussion

APRIL 18—*Section of Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] Calcareous tendinitis of the hand, William Cooper (by invitation), b] Low-grade multiple tuberculous lesions of bones and joints in children, Walker Eli Swift c] Occurrence of pseudarthroses in the Hibb's spinal fusion operation, Walter A L Thompson (by invitation), d] Analysis of causes of failure in arthrodeses of tuberculous joints, Ernest E Myers (by invitation), Discussion Joseph B L'Episcopo, David M Bosworth ¶ General discussion

APRIL 21—*Section of Ophthalmology* Executive session—a] Reading of the minutes b] Nomination of Section Officers and one member of Advisory Committee In memoriam—Herbert W Wootton—David H Webster ¶ Presentation of cases—a] Marginal dystrophy of cornea, William W Fitzgerald (by invitation) b] A case of lateral proboscis with a dermoyclops, Rudolf Aebh, Louise H Meeker ¶ Papers of the evening—a] Photoreceptors of vertebrates, S R Detwiler (by invitation), b] The ocular signs of intracranial saccular aneurysms, Frank B Walsh, Baltimore (by invitation) c] The surgical treatment of orbital plexiform neurofibromatosis, Edmund B Spaeth, Philadelphia (by invitation)

APRIL 22—*Combined Meetings—Section of Obstetrics and Gynecology, Section of Pediatrics New York Pathological Society and the New York City Committee on Prematurity* Executive session—a]

Reading of the minutes b] Nomination of Section Officers and one member of Advisory Committee, for each Section ¶ Papers of the evening—a] The pathology of the premature infant, Sidney Farber, Harvard Medical School (by invitation), b] The Chicago plan for reduction of infant mortality, Edith L Potter, University of Chicago, School of Medicine (by invitation) ¶ Discussion, Rustin McIntosh, Beryl H Paige, William E Studdiford

AFFILIATED SOCIETIES

FEBRUARY 17—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) ¶ Papers of the evening—a] Normal encephalogram, Cornelius G Dyke, b] Abnormal encephalogram and surgical findings, Leo M Davidoff (by invitation) ¶ Discussion, S B Wortis (by invitation), Bronson S Ray (by invitation), Thomas Hoen (by invitation), Louis Stevenson (by invitation) ¶ Executive session

FEBRUARY 27—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) ¶ Paper of the evening—Studies on the relation of the kidney to cardiovascular disease, M C Winternitz (by invitation), Yale University School of Medicine Discussion, Homer Smith (by invitation), Irving Graef ¶ Executive session

MARCH 17—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) ¶ Papers of the evening a] Tuberculosis of the breast treated by roentgen therapy, Samuel Richman b] Radium dosimetry according to the method of Paterson and Parker, Sidney M Silverstone (by invitation), c] Further experiences with contact (short distance) therapy, William Harris d] Treatment of cancer of the larynx (1) with fixed cord, (2) with subglottic disease, (3) total laryngectomy after radiation therapy, Rudolph Kramer ¶ Discussion, Edith H

Quimby, Carl Braestrup, John D Kernan, Maurice Lenz Executive session

MARCH 27—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) ¶ Papers of the evening—a] Histological changes produced in squamous cell epitheliomas of the mouth and oropharynx by fractionated external irradiation, John W Hall (by invitation), Milton Friedman (by invitation), New York University Medical College, b] Tumors of the eye, Algeron B Reese (by invitation), Institute of Ophthalmology of the Presbyterian Hospital Executive session

APRIL 21—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) ¶ Papers of the evening, a] A survey of radiation protec-

tion in forty-five hospitals, L Scheele (by invitation), D B Cowie (by invitation), b] X-ray protection in diagnostic radiology, C B Braestrup (by invitation) ¶ Discussion—a] Electrical protection, H B Williams (by invitation) b] Tube construction R R Michlett (by invitation), c] Protection with intermediate and high voltage, I H Blatz (by invitation), d] Protection with supervoltage, T R Folsom (by invitation) Executive session

APRIL 22—*The New York Pathological Society* (in affiliation with *The New York Academy of Medicine*), held a joint meeting with the *Section of Obstetrics and Gynecology*, the *Section of Pediatrics* and the *New York City Committee on Prematurity* See program under *Section of Obstetrics and Gynecology*

DEATHS OF FELLOWS

GILMOUR, ANDREW JAMES 121 East 60 Street, New York City, born in Fulton, New York, March 1, 1871, died in New York City, March 9, 1941, received the degree of Ph B from Yale University in 1895, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899, elected a Fellow of the Academy April 1, 1909

Dr Gilmour was consulting dermatologist to the Englewood Hospital and dermatologist to the Manhattan State Hospital He was a diplomate of the American Board of Dermatology, a Fellow of the American Medical Association, and a member of the State and County Medical Societies

WOOTTON, HERBERT WRIGHT Old Lyme, Connecticut, born in New York City, December 25, 1867, died in Old Lyme, Connecticut, February 28, 1941 graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1888, elected a Fellow of the Academy May 7, 1896 and served the Section of Ophthalmology as its Secretary from January 1906 to January 1909, and as its Chairman from January 1910 to January 1912

Dr Wootton was at one time professor of ophthalmology and director of surgery of the Manhattan Eye, Ear and Throat Hospital, and consulting ophthalmologist to the Willard Parker, Riverside and Gouverneur Hospitals, the U S Marine Hospital and the Kingston Avenue Hospital in Brooklyn He was a member of the American Ophthalmological Society, the New York Ophthalmological Society, the County and State Medical Societies of New York, and a Fellow of the American Medical Association

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



AUGUST 1941

PUERPERAL INFECTION

*A consideration of the relationship of pathological changes
and bacteriological findings to prevention and treatment**

WILLIAM E. STUDDIFORD

Professor of Obstetrics and Gynecology New York University College of Medicine

PUERPERAL infection may be defined as an invasion of the genital tract by pathogenic organisms during pregnancy, labor or the puerperium. Descriptions of this disease have been found in the earliest medical records and it has undoubtedly existed since the origin of the human race. Limitation of time prevents a review of the long history of the struggle of the physician to explain and conquer this most frequent complication of pregnancy and compels me to proceed at once to a discussion limited to certain aspects of this condition.

Before considering the disease itself it would be well to review briefly from the point of view of infection, the conditions which exist in the genital tract during pregnancy, labor and the puerperium under normal circumstances. The two chief points to be emphasized are the presence of organisms in or about the genital tract and the changes brought about by labor and delivery which favor the onset of infection.

* Read October 22, 1940 before the Graduate Fortnight of The New York Academy of Medicine.

Organisms have been shown to be present about and in the lower genital tract below the level of the cervical external os in all normal pregnant women. Staphylococci may be recovered from the skin of the vulva and perineum. *B. coli* may be found on the perineal skin and about the anus. The latter organism is not commonly found in the vagina unless marked relaxation of the perineum or urinary infection exists.¹ Present in the vagina itself may be found a variety of organisms, among which may be mentioned Doderlein's bacillus, indifferent aerobic streptococci, *Streptococcus viridans*, diphtheroids, anaerobic streptococci and other organisms. The anaerobic streptococcus is found very frequently^{2,3} and it has been stated by Hare⁴ that the vagina is the only situation in nature that this organism is found with any frequency. All investigators of the normal vaginal flora in pregnancy agree that hemolytic streptococci are rarely found, the incidence being usually stated at between 1 per cent⁵ and 3 per cent.⁶ It is also generally agreed that when these organisms are found to be present, evidence of pathogenicity, as shown by puerperal fever, rarely occurs. It has been shown that these hemolytic streptococci almost never belong to Group A, the cause of most human infection by this organism.⁶ Furthermore, it has been found that when virulent hemolytic streptococci are placed in the vaginas of experimental animals, they disappear with great rapidity.⁷

The genital tract above the external os must be considered as uncontaminated by bacteria. It is probable that the defensive activity of the tissue and the cervical mucous plug prevent their intrusion above this point. This statement is almost certainly true in the primipara but deep old cervical lacerations may permit some contamination of the canal in multiparae. The one exception that comes to mind is the individual who has a latent gonorrheal infection of the cervix during pregnancy. Certainly one must consider the cavity of the uterus and its contained ovum to be sterile above the level of the internal os during pregnancy. In the normal pregnant woman this state of affairs is disturbed by the onset of labor and this is particularly true if premature rupture of the amniotic sac takes place. Impelled by the uterine contractions, the presenting part, with or without the bag of forewaters, is forced down into the dilating cervix. The latter structure becomes separated from the adjacent membranes and the mucous plug is expelled. The presenting part with or without its covering of membranes becomes contaminated with vaginal organisms. During the period of uterine relaxation the presenting part

ascends carrying with it those organisms which contaminate the lower uterine segment. If the membranes are ruptured, the residual amniotic fluid likewise becomes infected. Occasionally the amniotic sac becomes infected without any evidence of preceding rupture, but ordinarily it is resistant to the penetration of organisms.⁸ This quality is of great value in limiting such bacterial invasion of the sac, following rupture, to the residual fluid and to the amniotic surface for a considerable period of time. The presence of bacterial invasion of the sac gives no clinical evidence of its presence for twenty-four hours or longer as a rule, but occasionally clinical reaction occurs much earlier. Microscopic evidence of inflammatory reaction in the membranes occurs very soon after such invasion takes place. Bacterial contamination of the amniotic sac rarely gives rise to serious or fatal postpartum infections in patients who deliver normally. They are, however, the most important factor in infection, usually of the peritoneal cavity, taking place after the performance of cesarean section. As evidence of the early bacterial invasion of the uterus during labor, Harris and Brown⁹ were able to obtain positive cultures in forty-four out of fifty patients at the time of cesarean section, these patients having been in labor six hours or longer. Anaerobic organisms were present in 45 per cent of the positive cultures.

As labor continues, the dilatation of the cervix gives rise to diffuse hemorrhage and edema, and causes minute lacerations of this structure. Occasionally deep lacerations may occur spontaneously. During the second stage, particularly in primiparae, hemorrhage and varying degrees of injury may occur in the vaginal mucous membrane. At the time of delivery the perineum is frequently injured by laceration or episiotomy. These points of injury offer possible points of entry for pathogenic organisms.

During the third stage of labor the placenta commonly detaches itself during the first few contractions following the birth of the fetus. It is expelled in a variable length of time stripping the membranes away as it leaves the uterus. Even if the membranes are contaminated with vaginal organisms, the mechanism of separation prevents the surface of the upper uterine segment from becoming inoculated immediately with bacteria. The postpartum uterus offers an ideal nidus for infection. In addition to the cervical injuries previously mentioned, the lining of the entire cavity above the internal os represents an extensive wound without epithelial covering. It is lined by the shaggy remnants of the decidua

where the membranes have been stripped away. Opening on the surface are the stumps of the basal glands, and numerous severed lymphatics and blood vessels. The placental site is represented by a round elevated area on the surface of which can be found the openings of large sinuses, some empty, some containing blood clot. The uterus is actively relaxing and contracting. During the early puerperium necrosis and shedding of the surface decidual remnants take place and following this the endometrium regenerates rapidly so that by the tenth to twelfth day the epithelial lining of the uterus is restored. The placental site remains, gradually becoming smaller and more constricted at its base, until at about the seventh to eighth week postpartum it is cast off, accompanied by a variable amount of bleeding.¹⁰ Extensive involution of the myometrium and vascular changes occur during this period.

While the lining of the upper segment should be sterile in the normal patient following the third stage, within a short time this area is invaded by organisms which are usually already present in the cervix and lower uterine segment. By the third day of the puerperium it is heavily contaminated.¹¹ In a group of thirty-seven afebrile postpartum patients, Douglas and Rhees¹ obtained 78.4 per cent positive cultures from the uterine cavity and found that 64.8 per cent of the cultures showed anaerobic streptococcus. Most of the remaining organisms belonged to the group commonly found in the normal vaginal flora. In the vast majority of patients this bacterial invasion gives no clinical evidence of its presence except for the lochial odor for which the putrefactive action of these organisms is responsible. These organisms rapidly disappear in normal patients as the endometrium regenerates. By the ninth day it has been shown that in 70 per cent of postpartum patients¹² the uterine cavity has become sterile.

Having considered normal pregnancy, labor and the puerperium as a nidus for infection, we may now review the pathological changes induced by infection and the pathways along which this process may spread.

Pathogenic organisms may gain entrance at any of the points of injury in the lower genital tract, almost always giving rise to localized wound infections in these areas. Rarely such an infection is serious in itself. One such patient has been seen with a suppurative thrombophlebitis originating from an infected perineum. She died of embolism and, at autopsy, the uterus and its vascular system were found to be free from

infection Lacerations of the cervix may become infected and such infection may spread through lymphatics into the base of the broad ligament producing pelvic cellulitis These types of infection are seldom serious except in that they may lead to infection of the uterus itself

Infection of the uterine cavity by pathogenic organisms gives rise to the majority of puerperal infections and almost all of the fatal ones The favorable field which this cavity presents has already been described The arrival of such organisms sets up an acute inflammatory reaction which may remain limited to the decidual remnants Deeper penetration of the uterine wall by such infection is favored by the multitude of open lymphatics and vessels Invasion of the uterine wall and the character of the cellular reaction is also influenced by the type of organism present An additional factor may lie in the contraction and relaxation of the puerperal uterus, an action which may serve to suck organisms into the open vessels

Most of our pathological knowledge of this condition is derived from the study of autopsies performed on fatal cases in which the infection has spread far past the uterine walls Holban and Koehler have analyzed a series of 163 such postmortems Sixty-four of these occurred in postpartum cases, ninety-nine followed abortion A summary of their findings by Eeles¹³ presents an excellent rapid review of the pathological findings and their interpretation and may be summarized in part as follows They show that infection usually starts within the uterus itself The appearance of the interior of the uterus varies In many cases (20 per cent) it is lined by a perfectly smooth normal-looking endometrium, with or without an apparently harmless piece of placenta attached to the wall, or it may show a patchy inflammation with fibrinous exudate not necessarily involving the retained piece of placenta or placental site Again the entire endometrium may be covered with a purulent exudate beneath which ulcers extend deeply into the uterine wall, an extreme stage of septic endometritis, or again the uterus may be large, soft, and flabby, its ulcerated walls covered with ragged decomposing tags of endometrium its cavity filled with dark green semifluid material with a foul odor This has been called putrid endometritis This is due to a secondary invasion of the uterus by anaerobes All stages may be found between this and septic endometritis While the putrid type is usually due to an infection with anaerobes and saprophytes and the septic to recognizably pathogenic organisms (the chief being streptococci), yet

mixed infection is apparently possible and frequent. The condition of the interior of the uterus does not always give the key to the character of the infection.

From this infected cavity the infection may spread in three different ways, either alone or combined with one another. These ways are (a) by blood vessels (veins), (b) by lymphatics, (c) by the tubes to the peritoneal cavity. A combination of all these methods of spread occurred in 71 out of 163 cases. A combination of (a) and (b) is most common. Extension by (c) is more frequent after abortion than after full time labor.

Venous Extension Spread by blood stream is quite common. In nineteen cases this type of spread alone occurred, in another thirty, the veins were involved but not alone. Infection spreads from the interior of the uterus through the veins of the uterine wall. On section the thick muscular wall frequently shows multiple small abscess cavities and the veins in its substance are large and contain fluid blood or infected thrombi. The process then reaches either the pampiniform plexus and the ovarian vein or the parametric venous plexus, the hypogastric vein and the common iliac vein. Which system of veins is affected depends upon the point of entry of the infection but no definite connection could be traced between any piece of placenta and the veins involved. When larger veins are cut open, the endothelial lining may merely be roughened, with perhaps a thrombus adhering to it or they may contain a bright red thrombus with specks of yellow pus throughout it, or they may be filled entirely with yellow green pus from which during life organisms could continually reach the circulation. Periphlebitis with abscess formation may occur at any point. These abscesses frequently involve the ovary or they may rupture into the peritoneum. If blood infection takes its own course, the next stage is the formation of metastases. They occur chiefly in the lungs, notably in the lower lobes. If an abscess reaches the pleura, it is likely to rupture and result in empyema. If the emboli are small, that is, composed of minute groups of bacteria, they are able to pass through the lungs and reach the left heart where they may cause endocarditis, or, passing still further on, give rise to multiple small abscesses in the cortex of the kidney and produce infarcts in the spleen. No case of spread of infection by the blood stream was found that did not have a definite phlebitis.

Lymphatic Extension Lymphatic spread through the uterine wall

to the cellular tissue of the parametrium occurred in no less than 115 cases. In forty-eight this was the sole method of extension. The uterine wall in these cases is hard and occasionally shows abscesses, multiple or single, which may rupture and cause peritonitis. If this does not happen, the infection reaches the enormous plexus of lymphatics in the parametrium. Frequently a massive hard edema accompanied by leukocytes and the deposition of fibrin takes place in this tissue. Sometimes the spread is rapid with only minimal tissue reaction. As the process continues, this cellulitis may extend upward behind the peritoneum on either side of the vertebral column or behind the colon, until it reaches the diaphragm, where huge collections of pus may accumulate, these are difficult to diagnose. Organisms may reach the thoracic duct directly by spread along the main lymphatics. Thence they gain entrance into the superior vena cava and general circulation. The emboli in this type of case are usually microscopic clumps of organisms and lung complications are less common, endocarditis more so, than in the blood-borne cases which show changes in the serous cavities i.e., meningitis with multiple abscesses in the pia mater, pericarditis, pleurisy, synovitis and peritonitis.

Spread by way of tubes Fatal spread by the tubes alone is least common and is chiefly found in abortion cases. The cause of death is peritonitis. The tubes are reached by direct surface spread from the endometrium. The inflammatory process in these fatal cases always extends too rapidly to allow the fimbria to adhere and occlude the tube. There is no enlargement of the tubes beyond simple inflammatory swelling. General peritonitis results and is rapidly fatal.

General peritonitis in puerperal patients is particularly fatal and it is not surprising that operation is usually hopeless in view of the post-mortem findings. Though many cases are of the diffuse purulent type, the loculated form is more frequent. Coils of intestine are glued together with abscess cavities in between, into these the bowel may rupture or abscesses form between the ascending and descending colon and the abdominal wall and, spreading upward, form huge subphrenic abscesses. The lymphatic form, when peritonitis is present, is rapidly fatal. Peritonitis may be associated with any of the forms of spread and was present in 69 of 163 cases.

Martland¹⁴ has analyzed the findings on 105 criminal abortions and has stated the cause of death to be peritonitis in 50 per cent, thrombo-

phlebitis in 31.4 per cent, and putrid endometritis in 7.6 per cent. The remainder died of an embolism or hemorrhage. His interpretation of the routes of spread are in the main similar to that set forth by Holban and Koehler. He also mentions direct extension of infection from the uterus to the peritoneum by perforating wound of the uterus. Such direct extension of infection is also responsible for peritonitis following cesarean section. It is usually immediate although it may occur some time after operation, due to disruption of the uterine wound. These represent the findings in the terminal stages of infection spreading from the uterus along various pathways in the relatively few fatal cases. One must remember that the spread of infection along these routes frequently is halted before reaching such proportions. Pelvic cellulitis without peritonitis or septicemia presents a favorable outlook. Many patients who present clinical evidence of thrombophlebitis recover.

Bacteriological investigation of patients with puerperal infection may be carried out by aerobic and anaerobic cultural studies of the uterine or vaginal discharges and of the blood. In the vast majority of instances, particularly in the milder forms of infection, such studies lead to confusing results. Most blood cultures are negative. The vaginal and uterine cultures often show a mixed group of organisms, many of which are similar to those found normally in the vagina. When a positive blood culture has been obtained one can be sure that one has identified the causative organism. When an organism is predominant or is present in pure culture in material taken from the vagina or uterus, this again is evidence, somewhat less strong, that the invader has been identified. Such positive findings are usually made in the more severe infections but even here one may fail to isolate the causative organism.

The organisms which are responsible most frequently for the more severe grades of puerperal infection are the streptococci, of which there are both aerobic and anaerobic varieties. Of the aerobic organisms some are non-pathogenic, others of mild virulence, while still others are the most rapidly invasive organisms known. After many attempts at classification a satisfactory method has been worked out. These organisms may be divided into alpha, beta, and gamma varieties on their cultural characteristics as grown on a blood agar plate. The alpha variety represents the organisms, such as *Streptococcus viridans*, which produce partial hemolysis, beta, those organisms producing complete hemolysis, and gamma, indifferent organisms producing no hemolysis^{15, 16}

Alpha and gamma varieties rarely are found in pure culture in the uterine or vaginal secretions and are usually associated with other organisms. Both types of organisms may be found among the normal vaginal flora. The *Streptococcus viridans* is associated with localized uterine infections and shows no marked invasive qualities. Occasionally it may set up a bacterial endocarditis in the wake of a puerperal infection, usually of the postabortal type. One severe and rapidly progressive infection caused by this organism has been seen on the wards at Bellevue Hospital, the patient dying of general peritonitis and septicemia following an induced abortion. At autopsy no endocarditis was found.

The most important organisms are the beta-hemolytic streptococci, not only in puerperal infection, but in human infection in general. These organisms have been classified into nine groups known as A, B, C, D, E, F, G, H and K, by Lancefield¹⁷ by means of a precipitation reaction. Applying this to a large number of hemolytic streptococci obtained from various types of human infections, it has been found that practically all of these organisms belong to Group A. In a few instances other groups such as B, C, D, and G have been found to be the infecting organism. Furthermore, it is possible to break down the groups into a number of different types by agglutination. Among the strains belonging to Group A, twenty-three different types have been found.¹⁸

The application of this method of classification to hemolytic streptococci obtained from puerperal infection has confirmed many old impressions and has yielded most important facts. As has been stated before, this method has shown that Group A organisms do not and probably cannot exist in the vagina under normal circumstances. Other studies have shown that almost 100 per cent of the beta-hemolytic streptococci recovered from puerperal infections belong to Group A.⁶ In a few instances other groups are found to be responsible, particularly Group B. These infections are usually mild although fatal infections are reported.¹⁹ Group A beta-streptococci have been recovered from the air and dust in the vicinity of infected patients.²⁰ They have been found present in the nasopharynx of a considerable percentage of normal individuals, and in a much higher percentage²¹ of individuals during or following acute pharyngeal infections. Finally in the majority of Group A infections investigated serologically, identical organisms have been found in the nasopharynx of an attendant, the patient herself, or in some other septic focus.^{22,23}

The significance of these findings may be briefly summarized as follows. Hemolytic streptococcus infections in the puerperal woman result from the introduction of an organism from Group A into the genital tract, almost always during labor and sometimes during the puerperium, from an outside source. This source may lie in the attendants, the patient, or in the surroundings of the patient. These infections may be called exogenous.

One may add a few words as to the behavior of these organisms *in vivo*. While less virulent strains tend to produce localized infections, the more virulent strains rapidly invade the lymphatic system and give rise to the fulminating sepsis, termed by Martland,¹⁴ "uterine erysipelas." Menkin²⁴ has shown that this characteristic is due to the lack of any localizing defense mechanism for forty hours, such as is found with staphylococcus infections where an immediate production of fibrin plugs in the lymphatics, coagulation of plasma and edema localize the organisms. This quality may be related to the production of fibrinolysin by the streptococcus.²⁵ Certainly experimental studies and clinical experience would lead one to believe that this organism tends to spread chiefly by lymphatics. That this is not universally true can be shown by the fact that venous involvement in streptococcus infections is noted quite frequently. It is believed that the severity of infection with this organism is due to the virulence of the strain rather than any immunological weakness in the individual attacked.²⁶

While this method of classification of the beta-streptococcus has been invaluable in making clear these facts, there are few institutions in this country where the technical assistance is available to carry out those complex procedures. From a practical point of view such cases can be discovered very rapidly by culture of the lochia on blood agar plates. Characteristic minute colonies surrounded by a wide zone of hemolysis appear within 12 to 16 hours, when the plates may be read grossly, the findings being later confirmed by microscopic examination. When such organisms are predominant or in pure culture and the patient shows a marked febrile reaction, one may be almost sure that one is dealing with a Group A beta-streptococcus and act accordingly. On the other hand when such colonies are present as a minority in the presence of many other organisms, febrile reaction in the patient usually is absent or present to slight degree. It is almost likely that these organisms belong to other groups than A. Positive blood cultures are only

obtained in serious infections and practically always indicate a Group A infection

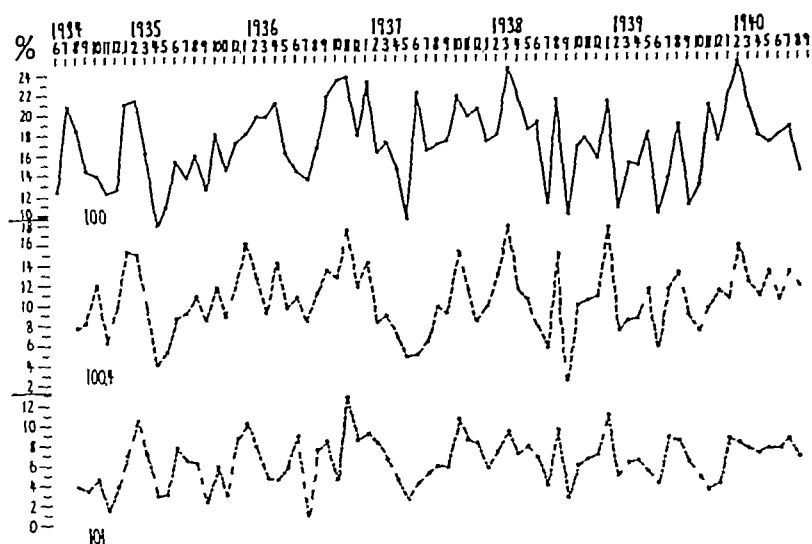
While Group A beta-streptococcus is the cause of severe sporadic puerperal infection and probably all epidemic puerperal infections, at the present time it is uncommonly the cause of such infection in New York City. Since 1933, 2600 lochial cultures have been taken on the Obstetrical Service at Bellevue Hospital from patients with fever or suspected infection. Sixty-nine of these cultures showed hemolytic streptococci, an incidence of 2.7 per cent. In only thirty-five of these cultures were hemolytic streptococci the predominating organism. On the Gynecological Service 622 cervical cultures were taken from patients suffering from abortion complicated by fever. Eighteen of these cultures or 2.9 per cent showed hemolytic streptococci. These organisms were not classified. Many of these patients showed no clinical evidence of the presence of a virulent organism, showing no fever or fever of slight degree and short duration. We feel justified in assuming that the incidence of Group A infections must fall well below 1 per cent. Watson states that only one severe Group A infection has been seen at the Sloane Hospital since 1936.²⁷ Douglas²⁸ states that beta-hemolytic streptococcus was found in only 1 per cent of the morbid patients at the New York Lying-In Hospital. While such infections are rare at present, there is no reason to think that this state of affairs is permanent, since the incidence may show a sharp increase at any time.

The anaerobic streptococci represent a group of organisms made up of a large number of strains. Attempts to classify these organisms with serological or biochemical methods have met with failure.²⁹ They can be classified by their cultural characteristics and gas production into four types.³⁰ This classification, however, has no particular clinical significance. They are strict anaerobes and anaerobic methods must be used to grow them in uterine or lochial cultures. The obtaining of positive cultures from these sources has no significance since they are present with a high degree of frequency in the normal vagina before labor,^{2,3} in the normal uterus postpartum¹ and in the same locations in febrile cases.¹ Attempts to prove the pathogenicity of these organisms has generally met with failure.³¹ It is, therefore, impossible to investigate the nature of this infection from an experimental point of view. Somner³² believes that the invasion begins by lymphatic spread. This is followed by involvement of the vein walls and, as a result of this, venous throm-

bosis This belief is borne out by the moderate parametritis present in thrombophlebitis and by the microscopic appearance of the involved veins In spite of lack of proof, an increasing number of observers are convinced that these organisms are responsible for a large proportion of puerperal infections^{30, 33, 34, 35} This conviction is based on the fairly frequent occurrence of cases of suppurative thrombophlebitis of the uterine veins accompanied by a bacteriemia with these organisms and the production of metastatic abscesses, chiefly in the lungs It must be emphasized that special anaerobic methods³⁰ must be used to grow these organisms from the blood While the factors which cause these organisms to take on pathogenic qualities are at present unknown, it is possible that trauma may contribute since most patients showing this type of infection have had mechanical interference in the delivery of the fetus Since the source of this infection lies almost certainly in the vaginal tract it may be properly called an endogenous infection

While the above-mentioned organisms are probably the chief offenders, nevertheless, one must remember that puerperal infection may be caused by many other bacteria The colon bacillus may be causative and is usually introduced by fecal contamination of the genital tract or because of an accompanying urinary infection Such infections are usually local although occasional cases of bacteriemia are observed Even when this organism appears in the blood stream, spontaneous recovery occurs as a rule Gonococcus is a fairly frequent cause of puerperal fever, the spread of infection upward from the cervix being favored by labor and the postpartum state These infections follow the characteristic course of gonorrheal salpingitis Staphylococcus infections are usually local but occasionally severe spreading infections develop with bacteriemia and multiple embolic abscesses Pneumococcus, gas bacillus, and *B typhosus* infections are occasionally seen All of them are probably conveyed to the vaginal tract during labor and delivery The source of the pneumococcus in the primary type of infection must undoubtedly be from the nasopharynx of patient or attendant In the secondary type, it is metastatic from a pneumonia Infections by the last two organisms result almost certainly from fecal contamination of the vaginal tract

The incidence of puerperal infection is usually determined by calculating the incidence of fever postpartum Since variations in standards and other factors make the exact determination of general incidence



MORBIDITY CHART

Chart I

difficult, figures from the Obstetrical Service at Bellevue Hospital will be quoted. The standard of morbidity used is based upon a fever of 100.4°F or more, persisting over twenty-four hours during the puerperium, excluding the first twenty-four hours after delivery. While this includes patients with fever due to other causes than genital tract infection, estimated to be from 10 to 20 per cent, it fails to include many mild febrile reactions due to genital infection. It may, therefore, be considered a fair rough estimate of the incidence of puerperal infection. In 11,400 patients delivered since 1933 the average incidence of fever of this degree has been 10.5 per cent. Chart I shows a graphic representation of the month by month variation of morbidity calculated on this standard as well as on similar standards based on 100°F and 101°F fever. It will be seen that the majority of these fevers are slight, only about 4 to 6 per cent of the patients showing fevers of 101° . It may also be noted that there is no marked evidence of seasonal variation although in some years the morbidity appears to be greater in the winter and spring months. This is in marked contrast to the severe hemolytic streptococcus infections observed on the Obstetrical Service and on the Gynecological Service following full term pregnancy and abortion. Those have invariably occurred between late November and early May. This corre-

sponds with the seasonal incidence of other hemolytic streptococcus infections, particularly of the nose and throat. This relationship may be taken as additional evidence of the almost certain source of these infections. Applying the stated standard of morbidity to this group, we find that 1180 patients had postpartum fever. The vast majority of these patients had fever of slight degree and short duration. No clinical evidence was present of spread of infection past the uterus. Even in severe infections only a minority gave any clinical evidence of spread. Relatively few could be classed as spreading infections. It is of interest here to note that Rivett³⁰ in an analysis of 533 severe cases found that 57 per cent appeared to be infections localized to the uterus.

During this same period there occurred fifty-three deaths, an incidence of 4.65 per thousand delivered patients. Seventeen of these deaths or 32 per cent were due to infection, an incidence of deaths from infection of 1.5 per thousand delivered patients.

Of the seventeen deaths, five occurred in patients delivered by cesarean section. All of them had general peritonitis, which began either immediately following operation or after a lapse of several days during which time there was evidence of a severe uterine infection.

Excluding the latter cases, there were twelve deaths among the vaginal deliveries. Among these is one patient with primary pneumococcus infection of the uterus with bacteremia and meningitis. Another showed a *Staphylococcus aureus* infection, bacteremia apparently arising from a thrombophlebitis of the arm on the seventh day postpartum in a patient who had a cesarean and hysterectomy for accidental hemorrhage. She had multiple transfusions, infection gaining entrance through one of these small wounds. Autopsy revealed a bacterial endocarditis. Two patients showed general peritonitis and bacteremia due to hemolytic streptococcus, the former diagnosis being verified at autopsy in one instance and at laparotomy in the other. Two patients did not come to autopsy. In one the exact type of sepsis is unknown. The other showed clinical evidence of a suppurative thrombophlebitis with no demonstrable bacteremia. Autopsy was performed on the remaining six cases. Two showed gangrenous endometritis and associated suppurative thrombophlebitis, while three showed suppurative thrombophlebitis, the uterus appearing comparatively normal. In two of these cases an anaerobic streptococcus bacteremia was demonstrated, and this organism was suspected as a causative agent in the other three. All of these patients

PRENATAL FACTORS RELATING TO MORBIDITY

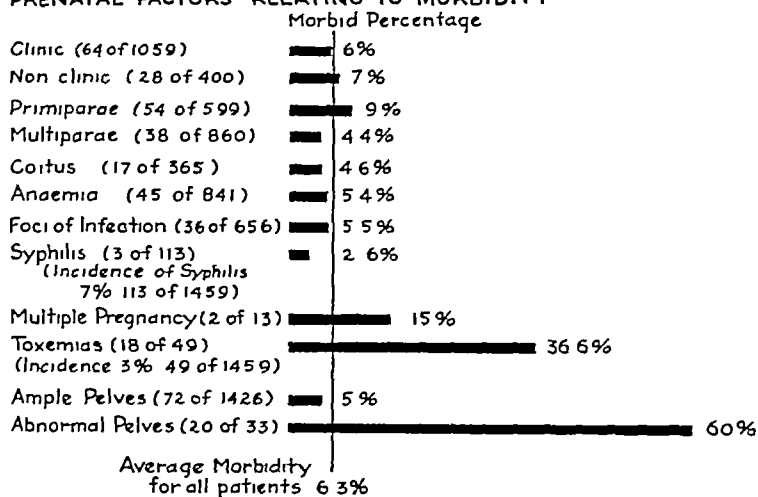


Chart II

showed pulmonary emboli or infarcts. In the last, the patient died a few hours after a long dry labor with intrapartum fever. She had an acute exacerbation of fever following delivery. Autopsy revealed nothing unusual but the blood cultures taken before death showed anaerobic streptococcus. The labors in the last group of six patients were marked by length, premature rupture of the membranes, amniotic sac infection, instrumental delivery, manual removal of the placenta, and tamponade of the uterus. Only one patient had a normal labor and delivery. Her infection was undoubtedly influenced by a pad accidentally left in the vagina. Rivett³⁸ has called attention to the high incidence of obstetrical interference in postpartum patients showing anaerobic streptococcus bacteriemia.

A group of these patients having a fever of 101° or more in the postpartum period have been analyzed by George Bowen in an endeavor to bring out factors occurring during pregnancy and labor which may be related to the appearance of postpartum fever. Chart II shows the antepartum factors. It will be seen that there is little difference between the patient who attends clinic and the one who does not. Primiparae show a higher incidence of fever than multiparae which may be related to the longer labor and the greater degree of trauma. A rather startling increase occurs among toxemias which may have some relation to their general condition and to a high incidence of interference. Patients with

INTRA-PARTUM FACTORS RELATING TO MORBIDITY

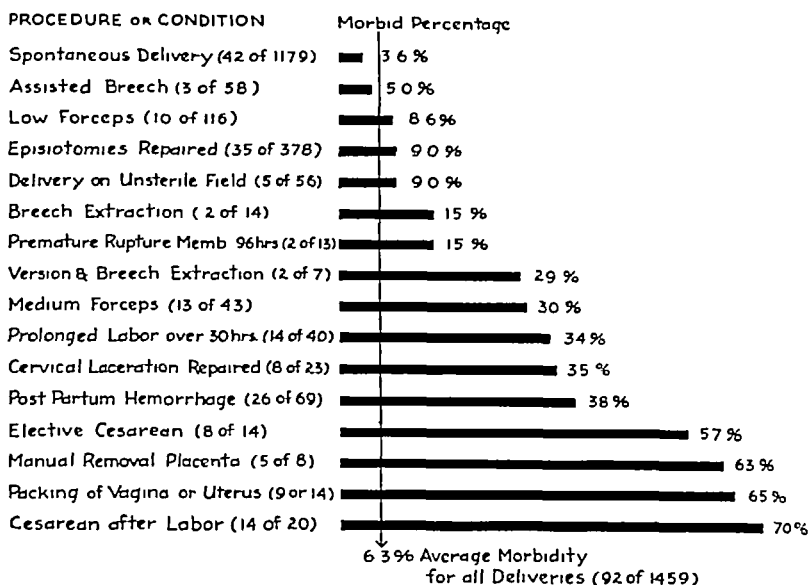


Chart III

abnormal pelvises show a very high rate probably due to prolonged labor and the high frequency of difficult operative deliveries. Chart III shows the intrapartum factors. It can be easily seen that with the exception of low forceps and breech extraction, all operative manipulation is accompanied by a great increase in morbidity. One cannot lay all the responsibility for fever on these procedures alone. Strict indications are laid down for their performance and in many cases the additional factors of prolonged labor, amniotic sac infection, and trauma, contribute to this increase.

This brief summary of the pathological and bacteriological features of puerperal infection, tinctured with some data on the background, incidence, severity and mortality gives us the fundamentals on which methods of prevention and treatment can be based. A consideration of these methods must be limited in this presentation to general principles.

Prevention is by far the more important field since by it alone are we likely to diminish the incidence and mortality due to postpartum infection. While difficult to prove, it seems quite obvious the pregnant woman in a perfect state of health at the onset of labor should be more resistant to infection than the women suffering from anemia, pyelitis, toxemia and other common antepartum complications. Close ob-

servation during pregnancy should lead to the control of many of these conditions. Careful study of the characteristics of the pelvis, and as a consequence, the consideration of possible difficulties during labor, should lead to an earlier decision as to whether certain patients should be delivered by cesarean section or allowed to go through labor. Here the various techniques of Roentgen pelvimetry are becoming of great aid to clinical judgment, particularly when utilized during labor. In other words, adequate antepartum care must play a part in the reduction of infection.

Since it must be generally admitted that most obstetrical patients suffering from complications of pregnancy and labor can be handled more efficiently and, as a rule, more safely in hospitals, a word may be said in regard to such institutions. Ideally an obstetrical hospital should be an entirely separate unit, with adequate facilities for completely separating patients showing evidence of postpartum infection from those who do not. The mingling of normal postpartum obstetrical patients with those suffering from general surgical and medical conditions is indefensible. When an obstetrical service is conducted as part of a general hospital, it should be placed in a part of the institution as remote as possible from wards containing patients suffering from acute infectious diseases. To send a patient to an institution which does not observe this fundamental in obstetrical organization is to invite infection.

Because the sources of infection are varied, it is obvious that the routes of infection and the methods of prevention must be different. As has been pointed out before, the sources of puerperal infection may be classed as exogenous and endogenous. The recent bacteriological studies lead to a clear-cut conception regarding prevention of the exogenous type, the commonest forms of which are caused by Group A beta-streptococcus and *B. coli*. They must be considered separately.

The principal sources from which Group A strains are derived in puerperal cases are from the nasopharynx of attendants or of the woman herself and from septic foci in fellow patients, members of the family, or herself. The source of such organisms and the method of transmission to the genital tract have been classified by Hare⁴ as follows:

A. Organisms derived from a preexisting infection in the neighborhood of the patient.

Transmitted by air-borne infection, by instruments or hands, by infection of the nasopharynx of the patient and transfer as under

- C, by contamination of hands of patient touching vulva
- B Organisms derived from the nasopharynx of an attendant
Transmitted by direct droplet infection, by direct droplet infection of the hands of the patient, by direct droplet infection of the throat of the patient and transfer as under C to the genital tract
- C Organisms derived from the nasopharynx of the patient herself
Transmitted by contamination of the hands touching vulva, by passage of organisms to the feces and subsequent contamination of the vulva during delivery, by passage of organisms by way of blood stream to placental site, by contamination of air and dust and transfer by air currents
- D Organisms derived from hands of the attendant
Transmitted by direct transfer to vulva
- E Organisms derived from the hands of the patient
Transmitted by direct transfer to vulva

It should be obvious since the above sources and methods of transmission are capable of demonstration, that an obstetrical technique can be devised to block this type of infection. The cardinal points of such a technique are that (1) delivery should be carried out in an environment free from infection, (2) doctors and nurses should refrain from practicing obstetrics when suffering from acute nasopharyngeal infections of any sort, (3) droplet infection from the nasopharynx of carriers to hand or vulva should be minimized by the adequate masking of both nose and mouth of all attendants during labor, delivery and the early puerperium, (4) scrupulous attention should be paid to surgical technique by both nurse and doctor during labor and delivery, and (5) patients should be warned against touching the vulva.

These same principals apply equally well to the prevention of the much rarer primary pneumococcus infections.

The prophylactic use of sulfanilamide in patients at term has been suggested and there is experimental evidence to show that it may be of value.³⁷ The infrequency with which Group A infections are encountered in this vicinity leads to the conclusion that this measure would not be practical under the present circumstances. The prophylactic use of this drug under epidemic conditions or in individuals who have been exposed to such infection when close to term is another matter. Here it may prove of great value.

The prevention of *B. coli* infections would appear to be mainly

one involving (a) the clearing up of urinary infections during pregnancy—sulfanilamide and the related drugs have proved of great value in accomplishing this end,³⁸ (b) an adequate preparation of the vulva before delivery, maintenance of an empty rectum during labor, and care to avoid contamination of the vulva with feces during delivery. Since the gas bacillus is also derived from the feces, this last group of measures applies as well to the prevention of infections by this organism.

While the principals of prevention in exogenous infections are quite definite, it is much more difficult to devise means of prevention of endogenous infections. The principal organism associated with this type of infection is the anaerobic streptococcus. As has been pointed out, these organisms are present in the vaginal tract of a large percentage of normal women before delivery, and in most instances, they give no evidence of pathogenicity in the postpartum period. Infections with this organism follow most often a prolonged exhausting labor, often with ruptured membranes, and usually terminated by difficult operative procedures. Two possible measures of prevention have been suggested. Careful antepartum study should anticipate a certain proportion of such labors and should lead to the decision to deliver the patient by cesarean section rather than by the vaginal route. It should be remembered, however, that such labors do not result merely from defects of the bony pelvis but also from variation in the soft parts, deficient pains and abnormalities of fetal presentation. Such a measure of prevention is easier to outline in theory than to put in practice. Early decision during labor as to the method of delivery and the choice of the proper type of cesarean section will minimize the danger of operation.

Another measure of prevention consists in the attempt to sterilize the vaginal tract during labor by various agents. Mayes³⁹ states that a marked lowering in morbidity has followed the use of mercurochrome instillations during labor. It has been shown that mercurochrome, merthiolate and other drugs markedly diminish the number of vaginal organisms.⁴⁰ Colebrook⁴¹ confirms this observation using a number of antiseptics, he points out, however, that the organisms rapidly reappear and that the new flora contains many organisms not present before. He feels that the use of such agents is of no value, and since they may injure the defense mechanisms of the vaginal mucous membrane, they may be harmful. On the other hand Brown⁴² reports that when vaginal instillations of acriflavine and glycerine are employed during la-

bor, there is a marked drop in positive cultures obtained from the lower uterine segment of those patients coming to cesarean section. As compared to an untreated series with 44 per cent positive cultures, he was able to show only 42 per cent. We have had no experience with the use of vaginal antiseptics during labor at Bellevue Hospital but feel that they may prove of value in diminishing the number of endogenous infections. This group of infections presents a host of unsolved problems to the investigator. Until some of them are solved, these infections cannot be controlled.

In conclusion let us consider the influence of pathological and bacteriological studies on the treatment of infection after it has taken place. Such treatment can be considered under two heads, surgical and medical. Surgical therapy involves relatively few procedures, the most important of which consist of hysterectomy, ligation of veins draining the uterus, drainage of peritonitis, drainage of parametrial abscesses and the removal of retained secundines. The inadequacy of some of these procedures, as shown on the autopsy table, together with the marked tendency of the individual to localize infection spontaneously and to recover, has led to the abandonment of some of these procedures. Hysterectomy is rarely performed in these patients and in the records of Bellevue Hospital for the past seven years only one such operation has been done for this indication. The patient had a degenerating fibroid, infected with *Staphylococcus aureus*, and recovered promptly after operation. After a trial, ligation of thrombosed veins has been abandoned because of the uncertainty as to the exact point to be attacked and because of dubious results. Most authorities advise against the drainage of general peritonitis arising from a uterine focus. Our own experience at Bellevue leads us to believe that this operation tends to hasten the fatal termination. Surgical intervention at present is limited to the drainage of localized peritoneal exudates and of parametrial abscesses. The latter procedure is particularly effective and usually leads to rapid recovery. Finally, one may mention the removal of retained placental fragments. These fragments are present far more often after early abortion than after full term delivery, and the factor of infection frequently complicates their presence. Many authorities urge extreme conservatism until all clinical evidence of infection has subsided for some time before resorting to surgical removal. On the other hand, the removal of these fragments from patients showing clinical evidence of a localized infec-

tion with organisms of low pathogenicity is followed by rapid recovery in most instances.⁴³ Such cases infected with Group A streptococci should receive chemotherapy as a preliminary to the surgical procedure.

The main features of general care of these patients consist in complete bedrest, fresh air, sunlight, ample diet, and expert nursing attention. The gastrointestinal disturbances secondary to a spreading pelvic infection may make necessary suction drainage of the stomach and intestinal tract and the use of parenteral fluids containing glucose and electrolytes. The marked anemia frequently observed in these infections must be combatted with repeated transfusions. Less effort is expended in the elimination of pelvic exudates since it has come to be realized that both the process of parametritis and of thrombophlebitis represent important defensive mechanisms which tend to limit the spread of organisms. Once the spread is limited and the full defense of the patient is mobilized, such exudates tend to disappear spontaneously, providing abscess formation does not take place. Patients seen a year after recovery from the most severe pyogenic puerperal infection rarely show on examination any evidence of any residual lesion.

In addition to the general care of the patient, many special forms of therapy have been employed in these infections. Vaccines, serums, and a host of drugs have been used only to be discarded as valueless. The advent of sulfanilamide and its related compounds is, therefore, a great advance.

However, it must be pointed out that these drugs are only of value in certain types of infection which, at present, constitute only a small percentage of the total number occurring in this region. To use them rationally an early diagnosis must be made as to the nature of the invading organisms. As has been pointed out before, this can only be done on the basis of a positive blood culture or on the finding of a predominant organism in the lochial or uterine culture. In the majority of instances, blood cultures are sterile and lochial and uterine cultures show a mixed group of organisms. The most frequent bacteremia observed in these patients at Bellevue Hospital is that caused by the anaerobic streptococcus, the second most frequent, that caused by the beta-hemolytic streptococcus. Colebrook reverses this frequency in his reports, which deal of course with much larger groups of cases.³⁰ Bacteremias caused by primary pneumococcus, by staphylococcus, by colon bacillus and by gas bacillus infections are rare. The beta-hemolytic

streptococcus is the commonest clear-cut infection to be detected by means of lochial or uterine cultures. As has been noted, it is rarely found at the present time. Gonorrheal infections are usually disclosed by the examination of direct smears from the cervix and urethra. Cultural methods are available, are more efficient, but have not yet proved suitable for use as a routine diagnostic measure.

Considering the value of chemotherapy on such infections, it may be stated, from the clinical and laboratory experience of the past few years, that such treatment is of great value in puerperal infections caused by the beta-hemolytic streptococcus, pneumococcus, staphylococcus and gonococcus. Such treatment has proved of no value in genital infections caused by the anaerobic streptococcus and colon bacillus. Doubt has recently been expressed as to the value of chemotherapy in gas bacillus infections.⁴⁴

The most important group of infections affected by these drugs is that caused by the beta-hemolytic streptococcus. One can classify patients showing this infecting organism into four groups: (a) Patients with positive cultures and no evidence of disease, (b) those showing positive cultures and slight degrees of fever, (c) those showing positive cultures, high fever but no evidence of spread past the uterus, and (d) those showing positive cultures, high fever, bacteriemia and other evidences of spread past the uterus. The latter types of cases may be called severe local and severe spreading infections. Chemotherapy should be limited to these two groups. Colebrook⁴⁵ reports a mortality of 22.8 per cent in patients with this degree of infection from 1930 to 1933. Since the advent of sulfanilamide this mortality has been reduced to 5.5 per cent. There are no reports in this country that can be compared to his, since no one observer has treated such numbers of this infection. Some idea of the infrequency with which severe infections with this organism are encountered at present may be gathered from the fact that in spite of careful search, one year elapsed before finding a severe hemolytic streptococcus puerperal infection at Bellevue Hospital to treat with sulfanilamide. Since this time we have seen eight cases of postpartum or postabortal sepsis with bacteriemia caused by this organism, all of whom have been treated with sulfanilamide. Five recovered and three died, a mortality of 37.5 per cent. Between January 1, 1933, and September 1, 1936, twelve such cases were admitted. Ten of these patients died, the mortality for the group being 83.3 per cent. While this

is a small series, nevertheless it shows a marked improvement in our results. Furthermore, all the patients with severe local infections have recovered and none have developed bacteriemia after treatment was begun. It is of interest that two of the patients who died showed suppurative thrombophlebitis of the pelvic veins and one, bacterial endocarditis. Lockwood⁴⁴ has pointed out that this type of lesion among others is not favorably affected by chemotherapy. Sulfanilamide, in our hands, has proved the most satisfactory drug for this type of infection. It can be used over long periods with relatively little disturbance of the patient. Time does not permit enlarging on the details of treatment which doubtless will be taken up by other speakers at this meeting.

A few brief remarks may be made on the other types of infection suitable for chemotherapy. Gonococcal infections respond readily in the majority of instances to sulfanilamide. In refractory cases additional treatment with sulfapyridine will often clear up this infection. The value of sulfapyridine in pneumococcus infections both with and without serum has been abundantly demonstrated and should be of value in both primary and secondary genital infections. We have had no experience in its use in primary infections. Sulfathiazole and sulfamethylthiazole appear to be better agents to use when staphylococcus infections are present. No opportunity for their use has presented itself at Bellevue, but I am acquainted with the details of one patient with puerperal septicemia in whom recovery took place under treatment with the latter drug.⁴⁵

One can say, then, that the advances in chemotherapy have been of great assistance to the obstetrician in the treatment of a small group of cases caused by certain specific organisms. Fortunately, in this group we find infections of the most severe and fatal type, notably the Group A beta-streptococcus. In the vast majority of puerperal infections a mixed group of organisms is present. In a few of these cases we know, and in a large number we have cause to suspect that the anaerobic streptococcus plays a leading part. There is no known agent which affects favorably infections caused by this organism. This may well be due to the type of lesion produced which is, in a high proportion of cases, suppurative thrombophlebitis. Perhaps some future discovery will produce a successful agent against this type of infection. At present we must rely entirely on prevention to diminish its incidence, severity, and mortality.

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BRUCELLOSIS*

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BRUCELLOSIS (undulant fever, Malta fever, Mediterranean fever, goat fever, contagious or infectious abortion of cattle, Bang's disease, Texas fever, Rio Grande fever, et cetera) is now known to be a common and widely distributed disease of animals and man. Our studies of this disease, begun in 1928, resulted in the discovery of ninety cases in and about Dayton during a period of eighteen months. In 1930, the author expressed the belief that brucellosis would soon become recognized as a major public health problem. That this opinion was justified has been abundantly substantiated by developments of the past decade.

The first cases of Malta fever to be recognized in this country occurred among men recently returned from the Tropics (Musser and Sailer, 1899). Craig (1905) not only detected many cases among men in the Army who had served in the Philippine Islands, but also established the diagnosis in a nurse who had never been out of the country and who had had no contact with patients with Malta fever. Craig suggested at this time that many patients with atypical typhoid-like fever might be suffering from Malta fever. A few cases of the disease were reported from goat-raising areas in Texas, New Mexico and Arizona by Gentry and Ferenbaugh (1911) and by Yount and Looney (1913). Then the disease apparently faded from medical consciousness for a decade, when Lake and Watkins (1922) published their startling report of an epidemic of Malta fever in Phoenix, Arizona, which they traced to the infection of raw goat's milk. Up to this time physicians naturally associated brucellosis only with a goat source. It was the monumental observation by Alice Evans (1918), that the organisms of Malta fever and contagious abortion of cattle were for all practical purposes indistinguishable, that led to the discovery of the widespread occurrence of *Brucella* infection of bovine and porcine origin.

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Following the first report by Keefer (1924) of a case of brucellosis due to the abortus variety of the organism, a rapid succession of reports of cases of bovine or porcine origin appeared from South Africa, Canada, Germany, Sweden, Norway, Denmark, Italy, Great Britain, Switzerland, The Netherlands, France, Puerto Rico and New Zealand. Subsequent reports leave little doubt that brucellosis is world-wide in its distribution and is most prevalent in those areas in which *Brucella* infection of cattle, hogs and goats is widespread.

For twenty-one years the *Micrococcus melitensis* of Bruce and the *Bacillus abortus* of Bang had been regarded as separate, unrelated species, until Alice Evans' observation that the two organisms are indistinguishable morphologically, biochemically, culturally, and by ordinary agglutination tests. The results of further studies led Evans to state that the two organisms probably possessed similar pathogenicity for human subjects. In 1927, Carpenter recovered an organism indistinguishable from *Brucella abortus* from the blood of ten human beings suffering from brucellosis, five pregnant heifers inoculated with these cultures promptly aborted. These observations of Evans and Carpenter have been confirmed by many workers throughout the world. It is now known that the organism which produces contagious abortion in cattle and other domestic animals is capable of producing in human beings a disease clinically and bacteriologically similar to the Mediterranean type of Malta fever.

Since Bruce had described the organism as a coccus and Bang had termed it a bacillus, it became apparent that the *melitensis*-*abortus* group of organisms should be reclassified. The proposal by Meyer and Shaw that the organisms should be designated by the generic name *Brucella* has met with universal approval. Consistent with this proposal, the name *Brucellosis* has been generally adopted as the single designation for the disease produced in animals and man by the *Brucella*. The organism usually associated with goat infection is termed *Brucella melitensis*, while the organism of infectious abortion of cattle is called *Brucella abortus*. Trium described a third related organism associated with the infection in swine, which has been designated *Brucella suis*.

Organisms which have been designated as caprine (*melitensis*) or porcine (*suis*) have been recovered from cow's milk. The antigenic differences are probably best explained on the basis of host adaptation. It seems probable that *Brucella abortus* is the primitive strain from which

other strains have developed as the result of passage through various animal hosts

The importance of brucellosis as a rapidly developing public health problem is vividly indicated by recent experiences with the disease in the United States. Prior to 1927, the sporadic cases which were encountered were regarded as clinical curiosities. Most of these were related to endemic foci of goat infection in Texas, New Mexico, and Arizona. During the years 1927 to 1930, the recorded cases numbered 217, 649, 1301 and 1385, respectively. During 1929, cases of brucellosis were encountered in every state of the Union. In 1940, 3358 cases were officially reported to the U. S. Public Health Service by State Health Departments. It is undoubtedly true that the number of cases actually occurring is much larger than that reported. Hardy reported the occurrence of 1669 cases in one state (Iowa) from 1925 to 1935. It has become more and more apparent that this rapid increase in the incidence of the disease has been due chiefly to infection of human beings with the organism of contagious abortion of cattle and hogs. American physicians soon realized that these observations provided an explanation for their failure to arrive at a confirmed diagnosis in many cases of typhoid-like and malaria-like diseases.

Among urban populations, the disease appears to be transmitted through the raw milk of cattle infected with *Brucella abortus*. Of the 220 patients with brucellosis studied personally by the writer, the ingestion of raw milk or unpasteurized dairy products containing the organism of contagious abortion of cattle was demonstrated to be the source of infection in the great majority of instances, these findings are corroborated by the investigations of Carpenter, King, Orr, Huddleson, Farbar, Mathews, Sensenich, Giordano, Ey and others. Hardy expresses the belief that direct contact with infected cattle and hogs has been responsible for a great number of cases of brucellosis occurring in Iowa. Hardy's investigations of 991 cases of brucellosis occurring in that State, led him to the conclusion that the *abortus* and *suis* species of the organism are about equally responsible for the brucellosis morbidity in the State. Hardy has demonstrated by animal experiments that the skin may act as the portal of entry of the organism. Morales-Otero, of Puerto Rico, has reproduced the disease in human volunteers by inoculations through abraded skin. It is apparent, therefore, that there are two important sources of infection for man, that is, the ingestion of raw milk

or unpasteurized dairy products containing *Brucella*, or direct contact with infected fresh animal tissues or discharges. There is no definite evidence of man-to-man transmission of the disease.

CLINICAL MANIFESTATIONS IN MAN

Because brucellosis presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases. Many physicians have arrived at a tardy diagnosis of brucellosis only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or x-ray evidence of tuberculosis. Less often, the disease has been confused with acute rheumatic fever, subacute bacterial endocarditis, bronchitis, pyelitis, appendicitis, cholecystitis, or tularemia.

SYMPTOMATOLOGY

As knowledge of the clinical manifestations of brucellosis has advanced, particularly during the past decade, it has become more and more apparent that the older text book descriptions of the symptomatology of the disease were based largely on experiences with brucellosis of goat origin. The classical clinical picture of a disease characterized by an undulatory, remittent, or intermittent fever, drenching sweats, chills, headache, backache, muscular and joint pains, weakness, loss of weight, possibly a palpable spleen, an infrequent skin eruption, leukopenia with lymphocytosis, and secondary anemia, pertains chiefly to the severe acute forms of the disease. In a high proportion of cases, the disease pursues a relatively mild, prolonged course, extending over many months or years. The early descriptions by Hughes and Craig included many such cases. Alice Evans and others have more recently directed particular attention to the common chronic ambulatory form of brucellosis in which the patient, whose spirits are already depressed by continued ill health, is often given further discouragement when a diagnosis of neurasthenia is made. Many "neurasthenics," whose chief complaints were exhaustion, insomnia, irritability, and a variety of aches and pains, have been found to be victims of chronic brucellosis.

Since the symptomatology of the acute and the chronic forms of brucellosis varies so greatly, these two manifestations will be considered separately.

ACUTE BRUCELLOSIS

The incubation period has been found to vary from five days to longer than one month. In accidental laboratory infections the incubation period has varied from ten to twenty days. The prodrome is not unlike that of any general infection, with a gradual onset, although in occasional cases the disease is initiated with a sharp chill and rapid elevation of temperature to 103-105 F (39.4-40.6 C). A sense of tiredness and weakness, loss of appetite, constipation, headache and backache are common early symptoms. Usually, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills or chilly sensations, nocturnal perspiration and weakness. The patient often feels quite well during the morning hours, particularly in the early stages of the infection. As the temperature rises, during the afternoon or evening, the symptoms gradually return and increase in severity. The nocturnal exacerbations of fever occasionally reach great heights (106-107 F, 41.1-41.7 C). There is often a remarkable disparity between the subjective sense of fever and the height of the fever as registered by the clinical thermometer, in many instances the patient does not complain of fever, nor does he present a febrile appearance, but the physician finds, to his surprise, a fever of 101-103 F (38.3-39.4 C). As the fever abates, chills and sweating occur. If defervescence is rapid, the perspiration is more likely to be of a drenching character. In such cases, the sweats, which literally saturate the night clothing and bedding, are one of the most impressive features of the disease. The perspiration often has a peculiar sweetish, fetid odor. The chills may be severe enough to be regarded as true rigors in about one-third of the acute cases. Many patients experience only mild chilly sensations, while in about one-fourth of cases chilliness is absent.

Arthralgia and muscular pains are prominent features of the acute form of the disease in approximately one-half of the cases. The joint pains may be more pronounced during the onset or they may persist throughout the course of illness. The myalgia may be accompanied by a feeling of "stiffness" not unlike the muscular soreness which follows vigorous exercise. Hydrarthrosis and transient periarticular swelling have been observed occasionally. Permanent impairment of the joints usually does not occur. Suppurative osteomyelitis as a complication of brucellosis has been described with increasing frequency during the past

few years. In most of the reported cases the vertebrae, particularly in the lumbar region, were attacked. In some instances other bones, such as the humerus, femur, skull and ribs, were affected. While the osteomyelitis sometimes occurred relatively early in the course of the disease, in most cases it was a late complication, occasionally occurring after apparent recovery from acute brucellosis. Feldman and Olson found similar examples of *Brucella* spondylitis in twenty-four hogs, an average occurrence of one in every 6000 swine slaughtered.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurs in some cases in which the fever reaches great heights. Regional *Brucella* localizations in the brain, spinal cord or meninges may occur during the acute phase of the disease and produce symptoms and signs of encephalitis, myelitis or meningitis, such complications are, however, more commonly observed as delayed manifestations of brucellosis. According to Roger and Poursines, whose recent classical monograph has aroused great interest in the frequency of central nervous system invasion by *Brucella*, the meningeal involvement predominates, and the development of encephalitis or myelitis, or both, is usually secondary to the meningitis. Because of this predilection for meningeal localization, Roger and Poursines have termed this form of the disease "meningoneuro-brucellosis." The involvement of the central nervous system may produce the first and only symptoms of the disease. The symptomatology varies greatly, depending upon the extent of meningeal invasion and the presence of additional complications involving the brain, spinal cord or peripheral nerves. In a patient with brucellosis, the development of such symptoms and signs as severe headache, vertigo, diplopia, nuchal rigidity, aphasia, psychic disturbances and various forms of paralysis, which are often evanescent, calls for examination of the cerebrospinal fluid. Characteristically, the spinal fluid will be under increased pressure and will show pleocytosis, increase of albumin and a decrease of globulin and sugar. Since the ultimate diagnosis during life depends upon the isolation and identification of *Brucella* from the spinal fluid, a particularly diligent effort should be made to recover the organism by culture and by guinea pig inoculation. DeJong has recorded eleven verified cases of *Brucella* meningitis or meningoencephalitis in which the organism was recovered from the spinal fluid by culture or by guinea pig inoculation.

The mitutinal remissions or intermissions and the nocturnal exacer-

bations of fever may last from one week to many months. The inadequate name "undulant fever" refers to recurring relapses of fever following afebrile intermissions. Such febrile relapses are the exception rather than the rule, most patients experience but one febrile period, lasting from a few days to several months, and finally reaching the normal level by lysis.

The essential gastrointestinal complaints are anorexia and constipation. The degree of constipation appears often to parallel the severity of the infection. Diarrhea is of rare occurrence. Nausea and vomiting may occur in the more severe cases. Abdominal pain is a not infrequent feature of the disease during its early manifestations. Among 125 cases studied by Hardy, abdominal pain occurred in forty, in ten it was the major complaint. Simpson found abdominal pain to be the chief complaint in sixteen of 142 patients with brucellosis. The occurrence of abdominal pain has often led to appendicectomy in patients with unsuspected brucellosis, the correct diagnosis having been made only after the persistence of febrile symptoms stimulated a further search for the cause. As in typhoid fever, the gall bladder may become a focus of *Brucella* infection. *Brucella* has been recovered from the excised gall bladder and from the bile following duodenal drainage in patients with symptoms of cholecystitis.

Symptoms referable to the respiratory tract may be an outstanding feature of the disease in certain instances. Cough, associated with mucoid or mucopurulent sputum production, is not infrequent during the first few weeks of illness, and may persist for months. Recent reports provide convincing evidence that pulmonary lesions of brucellosis are of frequent occurrence and are often detectable by roentgenographic examination, even in the absence of distinctive physical signs of pneumonia. The lesions most often encountered on x-ray examination are peribronchial infiltrations, hilar infiltrations, and scattered discrete or confluent patchy pneumonic areas. The pulmonary manifestations of brucellosis should be regarded as hematogenous lobular pneumonia rather than true bronchopneumonia. Without doubt, pulmonary lesions occur much more commonly than is generally realized. Serial roentgenographic studies will often provide an explanation for vague respiratory symptoms.

The most serious cardiovascular complication has been the occasional occurrence of vegetative endocarditis. Smith and Curtis found

reports of nine cases of *Brucella* endocarditis confirmed by postmortem examination, to which they added a similar case. In most instances the vegetations occurred on mitral or aortic valves previously damaged by rheumatic fever.

The name commonly applied to brucellosis of cattle, "infectious abortion," is derived from the well-known predilection of the causative organism for the genital tract. There is strong evidence that the same regional localization sometimes occurs in human beings. Painful swelling of the testes has been described frequently. Acute epididymitis, orchitis, prostatitis and seminal vesiculitis may be early manifestations of the disease. Simpson recovered *Brucella abortus* from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall.

There appears to be little doubt that brucellosis is at least an occasional cause of abortion in women who live on farms where they have direct contact with infected animals, or in women who consume raw milk or unpasteurized dairy products. There are reports of human abortion in which the history and serologic findings provide strong circumstantial evidence of the etiologic role of *Brucella*. In a study of 565 cases of brucellosis, Calder found a history of one or more miscarriages in 32 per cent of the married women, a history of one miscarriage followed by sterility was common, a few women reported as many as five or six abortions. More direct evidence has been provided by Carpenter and Boak who recovered *Brucella abortus* from the tissues of a human fetus which was aborted at the end of the fourth month of gestation. Kristensen isolated the abortus variety of the organism from the exudate which covered the uterine site of the placenta of a seven-month fetus. Frei isolated *Brucella* from the vaginal discharge of a woman who had aborted ten days previously.

Loss of weight is an almost constant feature of the acute form of the disease. The greatest loss, often from ten to fifty pounds, occurs in patients with high fever, drenching sweats and great prostration.

A transient cutaneous eruption, usually papular, macular or maculopapular, is a relatively infrequent finding. The skin lesions may simulate the roseola of typhoid fever.

CHRONIC BRUCELLOSIS

Many physicians feel that the symptoms and signs of acute brucel-

losis are often sufficiently characteristic to justify such a provisional diagnosis on the basis of clinical findings. In dealing with chronic brucellosis, however, the physician is often faced with a problem which will tax his diagnostic acumen to the utmost. No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations.

Quite naturally, a certain amount of wholesome skepticism has arisen in the minds of some physicians regarding any wide prevalence of chronic brucellosis. Such a feeling of doubt is quite defensible, since one is justified in questioning the validity of some of the diagnostic tests upon which such a diagnosis is often based.

The common and unfortunate employment of the name "undulant fever" has served only to add further difficulties in the recognition of cases of chronic brucellosis. A significant temperature curve, physical signs of disease, and positive agglutination tests and skin tests may be entirely lacking throughout a long period of chronic illness. The recent studies by Evans, Poston, Angle, Scoville, Thames, Calder, Hamman and Wainwright, Harris, and Cameron and Wells leave little doubt that a protracted, relatively mild form of brucellosis is widely prevalent and constitutes a major cause of chronic ill health. Only a small proportion of patients with chronic brucellosis, probably less than 10 per cent, have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis. In many cases the patient is not entirely incapacitated for work, but complains chiefly of weakness and exhaustion, with or without mild fever. Since the commonly employed diagnostic tests are frequently negative in such cases, and since even the most conscientious physician may not find physical abnormalities to account for the patient's complaints, the almost inevitable diagnosis of neurasthenia or psychoneurosis is too often made.

Surveys conducted in widely separated parts of the United States during recent years reveal that an ambulatory, partially disabling, chronic form of brucellosis is a widespread cause of prolonged ill health. Angle, Algie, Baumgartner and Lunsford found that 9 per cent of 7,122 school children gave positive reactions to the intradermal test, 79.3 per cent of the positive reactors consumed raw milk, a high proportion of the children had complaints consistent with the ambulatory type of brucellosis. Gould and Huddleson observed positive reactions in 845 of 8,124 persons (10.3 per cent) tested intradermally with brucellergen. Most of these individuals were residents of an infirmary for homeless

indigents and of a mental hospital where unpasteurized milk was consumed and where the supply of dairy products was obtained partly from a herd known to be infected with *Brucella*. Of the 845 reactors to the skin test only 111 (13.1 per cent) showed a positive agglutination reaction. The unreliability of the agglutination test in detecting chronic brucellosis has been noted by many other workers.

A recitation of all of the symptoms which have been ascribed to chronic brucellosis would serve only to heighten the confusion which as yet surrounds this baffling phase of the disease. In general, it may be stated that the three cardinal features of most cases of chronic brucellosis are weakness, low-grade fever and a lack of objective physical findings. McGinty and Gambrell have listed over 150 different manifestations of chronic brucellosis. Mild degrees of fever may be present for many weeks or months, there may be several months of complete freedom from fever, sudden febrile exacerbations may occur, accompanied by an accentuation of the prevailing symptoms, or by the development of evidence of new regional symptoms affecting the respiratory, cardiovascular, genitourinary, gastrointestinal, skeletal or nervous systems. Pneumonia, endocarditis, orchitis, epididymitis, prostatitis, oophoritis, cholecystitis, hydrarthrosis, arthritis, spondylitis, osteomyelitis, ocular complications or meningoencephalitis may be associated with the acute form of the disease, but much more commonly appear several months, or even years, after the often indefinite onset of the chronic form of brucellosis. In some instances such delayed evidences of regional *Brucella* localization may appear long after apparent recovery from the acute manifestations of the disease. All students of chronic brucellosis have emphasized the almost universal prominence of symptoms which relate to the central nervous system. In addition to the occasional acute invasion of the meninges, brain and spinal cord by *Brucella*, there is evidence that the endoantigen of *Brucella* organisms circulating in the blood has a toxic action upon the central nervous system. These observations led Evans to state "These facts challenge the right of a physician to make a diagnosis of neurasthenia—a diagnosis regarded as dishonorable by the patient, and also by his family, his employer and his friends—without considering, among other possibilities, the possibility of chronic brucellosis."

Chronic brucellosis should be suspected in all cases of so-called "fever of unknown origin." There are many reports of the isolation

of *Brucella* from the blood, urine, bile or from extirpated tissues in patients who have experienced unexplained, long-continued, low-grade fever for years Hamman and Wainwright reexamined thirty-six such patients, an accurate diagnosis was finally made on ten of them, three were found to have brucellosis

In contrast to acute brucellosis, it is of particular significance that chronic brucellosis has been recognized in relatively few areas in the United States The discovery of a large number of cases in these centers has been largely the result of a determined effort on the part of a few investigators to learn of the incidence of the disease in their localities It seems quite apparent that the vast majority of cases remain unrecognized, since the evidence at hand indicates that chronic brucellosis is widely prevalent in rural communities and in cities and towns in which raw milk is consumed

DIAGNOSIS

If brucellosis is given consideration in the differential diagnosis of all cases of febrile illness, especially in those in which the diagnostic criteria for typhoid fever, tuberculosis, influenza, malaria, chronic bronchitis, pyelitis, rheumatic fever or bacterial endocarditis are not convincing, the disease will be recognized with much greater frequency This is true in cases of vague, mild febrile disease as well as in those in which the clinical manifestations of brucellosis are more clearly defined In such cases it should become an established practice to submit 4 or 5 cc of the patient's blood, collected exactly as for the Wassermann test, to a laboratory equipped with the proper *Brucella* antigens, for the agglutination test The rapid macroscopic agglutination method of Huddleson is a simple and reliable procedure

Since it is exceedingly hazardous to base a diagnosis of brucellosis solely on clinical grounds, recourse must be had to laboratory diagnostic tests These procedures include (a) primary isolation of the causal organism by cultural methods from blood, spinal fluid, secretions, excretions, or excised tissues, (b) indirect recovery of *Brucella* by culture after animal inoculation, (c) the agglutination test, (d) the intradermal test, and (e) the opsonocytaphagic reaction

The only method by which the diagnosis of brucellosis may be completely established is by the *cultivation and identification of the organism* While cultural techniques have improved greatly during the past

few years, with a corresponding increase in the number of reported instances of recovery of the organism, the undertaking is often beset with difficulties and requires skill and, above all, patience. The *melitensis* and *suis* varieties of *Brucella* ordinarily grow readily under aerobic conditions, while the much more commonly encountered *abortus* variety requires an atmosphere containing 10 per cent carbon dioxide. The procedure used by Poston with notable success is as follows: 15 cc of blood are obtained from each patient by venipuncture and placed in a small flask containing 4 cc of sterile 2.5 per cent sodium citrate solution. Four flasks containing 100 cc of liver infusion broth of pH 6.8 are each inoculated with 2 cc of the citrated blood. The flasks are incubated at 37 C., two in the room atmosphere and two in an atmosphere containing 10 per cent CO₂. After four days' incubation, daily smears of the broth cultures are made and stained by Gram's method. If no organisms are seen in the smears after ten days' incubation, 5 cc of the original culture are transplanted to 100 cc of liver infusion broth every three days for two weeks. Original cultures and transplants are incubated for three weeks before they are reported as negative.

The guinea pig is the most suitable laboratory animal for inoculation. Poston inoculates three guinea pigs with blood from each patient, two are injected intraperitoneally with 2 cc each of citrated blood, one is inoculated in the groin with 1 cc of citrated blood. The animals are observed daily. Beginning two months after inoculation, tests for specific agglutinins and for cutaneous reaction to Huddleson's brucellergen are made at intervals of a few days. When both tests become positive the animals are killed. Animals which remain negative to the agglutination test and to the skin test are killed four and one-half months after inoculation. Liver infusion broth is planted with the guinea pig's blood and with pieces of organs and is subjected to the cultural procedures previously described. The cultures may then be differentiated into *abortus*, *suis* or *melitensis* varieties by the agglutinin-absorption technique, the bacteriostatic action of dyes, glucose utilization and hydrogen sulphide metabolism.

The most commonly used and the most reliable indicator of *Brucella* infection, in the absence of positive cultures, is the agglutination test. This is particularly true in cases of acute brucellosis, in which a high serum agglutinin titer will be found in a great majority of cases. Agglutinins may appear as early as the fifth day of illness, but ordinarily

are not found until the second week after the onset. In some instances, specific agglutinins may not appear for several weeks. One important source of difficulty in interpreting the results of agglutination tests is the fact that agglutinins may be persistently absent (in about 6 per cent of patients) or may be present in low titer in persons from whom *Brucella* has been cultivated. Another source of error in interpreting the agglutination reaction is the fact that the titer may remain at a high level for months or years after recovery. Then, too, some individuals exposed to the infection may develop agglutinins without notable illness. Furthermore, the level of the agglutinin titer may fluctuate widely on repeated testing. *These considerations call for the exercise of keen judgment in interpreting the results of the agglutination test. A person suffering from some disease other than brucellosis may have a positive agglutination test merely as the result of a previous symptomatic or asymptomatic Brucella infection.*

In the past, diagnostic significance has usually been attributed to titers of 1:80 or above. The choice of such an arbitrary diagnostic titer is not justified in the light of recent studies. In those cases in which the clinical manifestations suggest brucellosis, the absence of agglutinins or their presence in titers of 1:10 to 1:40 should stimulate further bacteriologic and serologic studies.

The difficulties which attend the interpretation of agglutination tests in cases of acute brucellosis are greatly multiplied in cases of chronic brucellosis. While the great majority of patients with the acute form of the disease reveal a positive agglutination test in high titer, a high proportion of patients with chronic brucellosis give repeatedly negative agglutination reactions or positive tests in low titer. In a group of twenty-eight cases of chronic brucellosis studied by Evans, 46 per cent gave a negative agglutination reaction.

The occasional cross agglutination of *Brucella* and *Bacterium tularensis* should be borne in mind. In cases of tularemia the relatively higher titer with the *B. tularensis* antigen and the usually typical history leaves little doubt as to the interpretation of the serologic findings. If the *Brucella* and *B. tularensis* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them.

While the agglutination test is undoubtedly of great value, its limitations must be recognized. Otherwise, errors will be made in two directions: first, the correct diagnosis of brucellosis may not be made because

too much reliance is placed in a negative test, or second, an incorrect diagnosis of brucellosis may be made in a person who has a residual agglutinin titer from a previous invasion by Brucella, but who is suffering from some other disease when the test is made

The intradermal test is used to determine cutaneous hypersensitivity to specific Brucella antigen. A positive allergic skin reaction is generally accepted as evidence of past or present Brucella infection. While the great majority of patients from whose blood Brucella has been recovered show a positive skin test, the test has yielded negative results in rare instances in which Brucella infection was proved by culture.

The chief sources of error in interpreting the significance of a positive skin test lie in the fact that the test is frequently positive in exposed individuals with no history of an illness compatible with brucellosis. Furthermore, the hypersensitivity, once acquired after symptomatic or subclinical infection, usually persists for many years. *Therefore, it must be emphasized that a positive skin test does not mean that the symptoms from which the patient is suffering at the time of a positive skin test are necessarily due to brucellosis.* Students of this disease are only too familiar with instances in which a diagnosis of brucellosis was made only on the basis of a positive skin test and in which further developments revealed the presence of some such disease as active tuberculosis, Hodgkins' disease, leukemia, typhoid fever, malaria, or subacute streptococcic endocarditis. The intradermal test is regarded by Evans as a less accurate indicator of present infection than the agglutination test because the allergic state usually develops later than agglutinins and because it is generally retained for longer periods after recovery. Gould and Huddleson regard the skin test as the most sensitive diagnostic test for brucellosis, these investigators express the belief, shared by many others, that if the skin test is negative, brucellosis may usually be ruled out.

A variety of antigens has been used for skin testing. The two agents most commonly employed are (1) a heat-killed suspension of Brucella in physiologic saline solution (vaccine) and (2) a suspensoid of nucleo-protein isolated from Brucella by chemical separation, known as Brucellergin (Huddleson). If commercially available vaccines are used for skin testing, the usual procedure is to dilute the vaccine in a proportion of one part vaccine to nine parts sterile physiologic solution of sodium chloride and to inject 0.1 cc. of the diluted suspension intracutaneously in the ventral surface of the forearm. It is important to select properly

found that a significant proportion of patients yield aberrant and unexpected results in relation to their immunity status when the opsonocytophagic test is employed in conjunction with cultural methods, agglutination tests and skin tests. High phagocytic titers (immune reactions) occur in some patients with severe and uninterrupted brucellosis, proved by cultures. Certain recovered patients, asymptomatic for months or years, exhibit marked fluctuations from month to month, running the entire gamut from high to low phagocytosis, or sometimes none at all. *Until more extensive studies have been made on culturally proved cases of brucellosis the results of the opsonocytophagic test should be interpreted with caution and with reservations.*

Hematocytologic studies indicate that leukopenia occurs in the majority of patients with acute brucellosis. In chronic brucellosis, either leukopenia, moderate leukocytosis or normal leukocyte levels may be found. Calder has directed particular attention to the occurrence of active lymphocytogenesis as the most striking and constant feature of the blood picture in all of the manifestations of brucellosis. The lymphocytosis is evidenced by an increase in both percentage values and in absolute numbers of lymphocytes and by an unusually high proportion of immature lymphocytes (lymphocytic shift-to-the-left). Mild anemia of the macrocytic, hyperchromic type is the rule. The erythrocyte sedimentation rate is usually not high, except when complications are present. Calder expresses the belief that this combination of white blood cell and red blood cell abnormalities is distinctive for brucellosis and provides an additional confirmatory diagnostic aid.

A lowered basal metabolic rate, vascular hypotension, gastric hypochlorhydria or achlorhydria are commonly observed in patients with chronic brucellosis.

In the acute form of the disease the manifestations are often sufficiently characteristic to justify a provisional clinical diagnosis of brucellosis. The disease has been recognized most frequently in those areas in which investigators have stimulated their medical colleagues to search for it. Many victims of the disease do not appear dangerously ill and there is often a natural tendency to neglect the taking of a detailed history and the performance of a thorough physical examination.

Just as the diagnosis of brucellosis may be missed by too great reliance on any one or all of the diagnostic tests, so also is there danger that the diagnosis may be made much too freely by unjustified reliance

on a positive skin test This hazard pertains particularly to the diagnosis of chronic brucellosis

PROGNOSIS

Fatal outcome is rare, having occurred in about 2 per cent of reported cases During 1936, 107 deaths from brucellosis were officially recorded in the United States The importance of the disease is not to be judged by the low mortality rate The prolonged course and the resulting chronic ill health in a high proportion of cases make the outlook much more serious than the death rate would indicate Death is usually the result of overwhelming acute infection, terminating fatally during the first few weeks of illness, or it follows a relapse at any stage of the disease due to regional localizations of *Brucella* in such structures as the meninges, brain, heart valves or lungs

TREATMENT

The most important consideration in the control of brucellosis is prophylaxis The widespread distribution of the infection among cattle renders it difficult to control the infection at its source Many cows have Bang's disease and eliminate the organisms in large numbers in the milk and vaginal discharges without manifesting symptoms of the disease (abortion, mastitis, sterility and lessened milk yield)

Since 1934, the United States Department of Agriculture has been engaged in a laudable campaign directed toward eradication of brucellosis in cattle After fifty-five months of diligent effort, ending January 31, 1939, more than a million and a half cattle (approximately 55 per cent of the number tested) were found to give positive tests for brucellosis, the infected cattle were condemned and the farmers and dairymen received indemnities to compensate for the loss of the cattle Unfortunately, no similar campaign has yet been inaugurated to control the disease in hogs and goats

There is but one logical method for preventing the transmission of milk-borne infection to human beings, and that is by pasteurization Brucellosis is only one of the formidable list of diseases transmitted to man through the use of raw milk and other unpasteurized dairy products Murray, McNutt and Purwin, Boak and Carpenter, and Zwick and Wedeman have demonstrated that complete pasteurization (143-145 F

(61.6-62.7 C) for thirty minutes) will destroy *Brucella*. The need for strict supervision of the pasteurization process is apparent. For the protection of the health of those persons whose occupations bring them in direct contact with infected animal tissues we must rely upon education and the institution of precautionary measures.

For those persons who live on farms, or in small communities where pasteurization is not yet practiced, home pasteurization may be carried out by placing the milk in an aluminum vessel and heating it to 68.3 C, stirring constantly, then immediately setting the vessel in cold water and continuing the stirring until cool.

The general management of the patient with brucellosis will be largely determined by the prevailing symptoms and signs. General therapeutic considerations will vary greatly in individual patients. The therapeutic program for patients with acute brucellosis is quite different from that employed for the chronic form of the disease.

In severe cases of acute brucellosis, the general supplementary management is essentially that employed for any acute febrile disease, characterized by fever, chills and sweats. If the sweating is of a drenching character special provisions should be made for the protection of the mattress and for changes of bed linen and gowns. If the fever exceeds 104 F (40 C) tepid sponge baths are indicated, *antipyretic drugs should be avoided*. The patient should remain constantly in bed during the febrile phase and for at least one week after the temperature has returned to the normal level. Skilled nursing care is an essential requirement in the severe cases. The same precautions should be taken as regards the disinfection of urine and feces as in cases of typhoid fever. As the fever abates, a liberal diet of high caloric value is required, particularly for patients who lose considerable weight. The patient should be cautioned against resuming even moderate activity until there has been an appreciable gain in strength. Two or three additional weeks of rest will often save the patient from several months of partial disability.

In cases of chronic brucellosis, the general management must be strictly individualized. Since most of these patients are ambulatory and are at least attempting to perform some work, often at great effort, the program should be directed towards a maximum amount of rest. This may entail a regulation of the hours of work in order to avoid excessive fatigue. Since most of these patients suffer from the symptoms ordinarily ascribed to neurasthenia, a generous amount of practical psycho-

therapy, largely directed towards reassurance, is a fundamental requirement. The members of the patient's family should be fully informed as to the nature of the illness in order to enlist their sympathetic understanding and to avoid their stigmatizing the patient as neurotic or as a malingerer. The common symptoms of headache, backache, joint and muscle pains, insomnia, anorexia, constipation and anemia usually yield to appropriate symptomatic measures.

SPECIFIC THERAPY

While there is considerable evidence that the employment of various types of serum therapy and vaccine therapy has greatly improved the outlook for most patients suffering from acute or chronic brucellosis, it is extremely difficult to evaluate the effectiveness of any form of specific therapy in a disease characterized by natural remissions and by an extremely variable symptomatology. The reported results of vaccine therapy or serum therapy run the entire gamut from pessimism to hyper-enthusiasm. More extensive controlled and systematic studies on a large number of patients, carried out over a period of many years, are necessary before definite statements can be made. It would appear, however, that sufficient data have been accumulated to justify the continued and extended use of some of the specific agents.

A SERUM THERAPY

Interest in serum therapy, which had waned following the earlier appearance of several unfavorable reports, has been revived by the development of a more potent anti-*Brucella* serum by Foshay and his associates at the University of Cincinnati. Detoxified *Brucella* antigens are employed for the development of the antiserums in goats or horses. Several favorable experiences with the Foshay serum have been recorded by other workers. This type of antiserum therapy should be restricted to patients with acute or subacute brucellosis, preferably to those who have had the disease less than eight months. The dosage recommended by Foshay is as follows. For adults suffering from moderately severe to severe manifestations of the disease, the average total dose is 60 cc., given by three daily intravenous or intramuscular injections of 20 cc. each or by two daily injections of 30 cc. each, in unusually severe infections, 90 to 120 cc. may be given in unit doses of 30 cc. during a period of forty-eight to seventy-two hours, for children, a total of 20 to 30 cc.

may be given, either intramuscularly or subcutaneously, in daily doses of 10 cc each

Serum therapy is not indicated in cases of chronic brucellosis of more than eight months' duration, unless sudden, severe exacerbations occur. Such abrupt relapses are usually the result of regional localizations involving the meninges, brain, spinal cord, heart valves, lungs, liver, spleen and bone marrow. In such cases, the dosage of serum would be that recommended for unusually severe infections.

Scattered reports of the use of convalescent human serum, blood transfusions from recovered donors, or immunotransfusions from donors who have received prior injections of heat-killed *Brucella*, have appeared. Even though the number of cases is small and the period of observations not sufficiently long for accurate evaluation, the results were sufficiently gratifying to justify further trials, particularly as regards immunotransfusions.

B VACCINE THERAPY

It seems probable that the earlier discrepant reports of the effectiveness of vaccine therapy had their basis in a lack of standardized methods for the preparation of the vaccines, both as regards the choice of suitable strains and the concentration of the vaccine. These difficulties appear to have been largely overcome in recent years by the development of better standards for the preparation of therapeutic vaccines.

Brucella melitensis (varieties *abortus* and *suis*) vaccine, N N R, has been widely employed and is available through the usual trade sources. This vaccine is a saline suspension of heat-killed or formalin-killed *Brucella abortus* and *suis* organisms in equal quantities. Vaccines prepared from the *melitensis* variety of the organism should be utilized only in the treatment of the relatively rare *Brucella melitensis* infections.

Experience has taught that no rigidly standardized scheme of dosage of vaccine is applicable to patients with brucellosis. Experience and good judgment are essential requisites in determining the proper dosage for each individual. The usual procedure with the commercially available vaccine is first to test for hypersensitiveness by injecting 0.05 cc of a 1:10 dilution of the vaccine intracutaneously. If the patient does not experience an excessive local or systemic reaction within the next forty-eight hours, an initial therapeutic dose of 0.25 cc is injected into the deep subcutaneous tissues, or preferably into the muscle. Local reactions are minimized by intramuscular injections. If no untoward reaction fol-

lows the first injection of 0.25 cc, a second dose of 0.25 cc is given three days later. The dosage is then increased in increments of 0.25 cc, at intervals of three days, until a dosage of 1 cc is reached. Ordinarily, two injections of 0.5 cc and two of 0.75 cc are given before the 1 cc dosage is attained. Five to eight injections of 1 cc each may then be given at three-day intervals.

If the patient is highly sensitized, it is wise to begin with intramuscular doses of 0.1 cc, or, in rare instances of extreme sensitization, with doses of 0.1 cc of a 1:10 to 1:100 dilution of the vaccine, and gradually increase the dosage by 0.1 cc increments until a dosage of 1 cc is reached. If, during the course of vaccine injections an unusually severe local or systemic reaction should occur it is desirable to reduce the next dose to one-half the amount which produced the severe reaction and then cautiously and gradually increase the succeeding doses.

A series of four to six or more sharp systemic, febrile reactions, usually accompanied by a transient exacerbation of symptoms, is the goal of the treatment. Hence, only extreme local or general reactions should be avoided. Elevations of temperature to 103-105 F (39.4-40.6 C) are not uncommon within four to eight hours after the injection of vaccine. Such systemic responses may occur following the first injection of a small quantity of vaccine or may not occur until relatively large doses are given. In chronic brucellosis larger doses of the vaccine may be required, if no reaction is provoked after five or six 1 cc injections, the dosage may be gradually increased by 0.5 cc increments to 2 or 3 cc.

While some patients who have obtained an apparently satisfactory response to vaccine therapy have had little or no thermal reaction, the most prompt and lasting results have occurred in those who have experienced several such reactions.

Erythema and tenderness at the site of vaccination occur commonly for a day or two following injections. In about 5 per cent of cases, a local hard tumefaction may persist for much longer periods. In a small proportion of such cases sterile abscesses or local areas of necrosis have developed.

C BRUCELLIN THERAPY

Brucellin is a fraction of *Brucella* cells obtained by growing the organism in liver broth. The bacteria-free active agent is recovered from the liver broth filtrate. This preparation was devised by I. F. Huddleson and may be procured at the Central Brucella Station, Michigan State

College, East Lansing, Michigan

The dosage of Brucellin must also be adjusted to suit the requirements of individual patients. After the extent of sensitiveness has been determined by the intradermal injection of 0.1 cc of Brucellin, the usual procedure in non-hypersensitive patients is to give repeated injections of 1 cc at intervals of three days until the morning and evening temperatures between the intervals of injection tend to become subnormal. Here again, one object of this form of therapy is the production of a series of four or more febrile, systemic reactions. If the duration of illness is less than ten weeks, the likelihood of recovery following four 1 cc injections is greater than if the duration is longer than ten weeks. Patients with long-continued chronic brucellosis require a larger number of injections and may require gradually increasing amounts up to 5 cc before satisfactory reactions are produced. In highly sensitized persons, it is advisable to start with intramuscular doses of 0.1 cc. If there is no severe systemic reaction following this injection, each succeeding dose may ordinarily be doubled, until the larger dosage is attained.

In children, the initial dose of Brucella vaccine or Brucellin should not exceed 0.1 cc and succeeding doses should be increased by not over 0.1 cc increments. Considerable dilution of the vaccine is required for hypersensitive children.

A partially oxidized detoxified vaccine, devised by Foshay and O'Neil has been used with apparent success. Much smaller doses are given subcutaneously at more frequent intervals. The few reports of results indicate the recovery rate equals that of other vaccines or Brucellin. Local or constitutional reactions do not occur with the oxidized vaccine. It has been recommended chiefly for the treatment of chronic brucellosis.

While it is difficult to evaluate the results of vaccine or Brucellin therapy, the experiences of many investigators indicate that about 60 per cent of patients with brucellosis obtain apparently complete recovery after a satisfactory course of either agent. An additional 25 per cent appear to obtain some benefit, while the remaining 15 per cent are not improved.

The contraindications to vaccine or Brucellin therapy are heart disease, renal disease, arteriosclerosis, meningeal or cerebral localizations of Brucella or the acute fulminating (malignant) form of the disease.

NON-SPECIFIC PROTEIN THERAPY

Injections of foreign protein substances, such as sterile skimmed milk, typhoid vaccine or typhoid-paratyphoid vaccine have been utilized for the production of non-specific shock reactions in the treatment of brucellosis Erwin and Hunt reported good results in twenty patients with acute and subacute brucellosis following the intravenous injection of killed typhoid-paratyphoid organisms The usual initial dose was 30 to 50 million killed organisms, with two to six additional injections, increasing the dosage by increments of 25 million organisms

CHEMOTHERAPY

Neoarsphenamine, mercurochrome, acriflavine, metaphen, thionin, methylene blue, methyl violet, gentian violet and other chemical substances have been used in the treatment of brucellosis In most instances the reports of the apparently successful use of these substances were based upon observations limited to small numbers of patients The very length of the list argues against the specificity of any of them

Sulfanilamide and related compounds have been heralded as effective agents in the treatment of brucellosis since 1936 After the first wave of enthusiasm, usually based on short observations on relatively few patients, other reports of less favorable or entirely negative results have appeared Blumgart and Gilligan analyzed the results reported in the thirty-one papers which appeared between 1936 and 1939 Twenty-four of the reports were concerned with only one or two patients Of the seventy-four cases treated with sulfanilamide or allied compounds, there were sixty-eight apparent recoveries and six failures, fourteen of the sixty-eight patients (20 per cent) exhibited relapse after apparent recovery The daily dosage of sulfanilamide employed in most cases was 4 to 6 gm (60 to 90 grains) during the period of fever, with gradually diminishing dosages for three or four days after the fever abated The administration of the drug was rarely continued for more than twelve days Bynum reported six cases of brucellosis unsuccessfully treated with large doses of sulfanilamide Long and Bliss report recurrence of infection in four of five patients whose immediate response to sulfanilamide therapy was apparently quite satisfactory, in two instances *Brucella* was recovered from the blood after sulfanilamide therapy was discontinued The writer has had similarly disappointing experiences in several cases treated with large doses of sulfanilamide, controlled by

determinations of the sulfanilamide concentration of the blood *Until more extensive and extended studies are made on culturally proved cases, the value of sulfanilamide therapy in cases of brucellosis must be regarded as undetermined* In this connection it might be well to recall the fact that a temporary remission is not synonymous with cure

ARTIFICIAL FEVER THERAPY

The observation that recovery from brucellosis often followed the induction of fever by chemical or biological agents led Prickman and Popp to investigate the possible usefulness of artificial fever induced by physical means in the management of brucellosis Each of three patients was given three artificial fever treatments, each of five hours' duration, at a rectal temperature of 105-106 F (40.6-41.1 C), all were benefited by the treatment Zeiter described a similarly favorable experience More recently, Prickman, Bennett and Krusen analyzed the results of treatment with physically induced hyperpyrexia in twenty-one cases of brucellosis, apparent cure resulted in 80.9 per cent of the patients The duration of the disease prior to artificial fever therapy varied from ten days to two and one-half years The authors expressed the belief that fever therapy was most efficacious in the acute and subacute febrile stages of the disease Simpson, who has had similar favorable results, reserves artificial fever therapy for those refractory patients who do not respond to vaccine therapy Artificial fever therapy should be carried out only in properly equipped institutions by thoroughly qualified physicians and nurse-technicians

MISCELLANEOUS THERAPY

Since some degree of anemia is a common finding in brucellosis, it should be combated with appropriate dietary, iron or liver therapy Repeated small transfusions (200 cc) are of value in the management of the more severe grades of anemia In the more chronic forms of the disease, in which severe anorexia is a prominent feature, vitamin deficiency is common Large doses of vitamin B, with reinforcement of vitamin A, C and D intake, have been effective in relieving this distressing symptom

SUMMARY AND CONCLUSIONS

1 The author's prediction of a decade ago, greeted with some skepticism at that time, that brucellosis would become recognized as a public health problem of major proportions has been fulfilled Of the

220 cases of brucellosis studied by the author, all but 24 occurred prior to the passage of a universal pasteurization ordinance in 1931. In each of the 24 cases occurring during the past nine years the patient had consumed raw milk elsewhere prior to the onset of illness.

2 The symptomatology of the acute and the chronic forms of brucellosis varies greatly. The diagnostic criteria for acute brucellosis are usually not applicable to the chronic form of the disease. There is little doubt that the chronic ambulatory form of brucellosis is widely prevalent, is often confused with other diseases, and frequently is not recognized. Many "neurasthenics" and patients with so-called "fever of unknown etiology" have been found to be victims of chronic brucellosis. Less than 10 per cent of patients with chronic brucellosis have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis.

3 The only diagnostic procedure by which the diagnosis of brucellosis may be established with certainty is by the cultivation and identification of the organism. The agglutination test and skin test are of considerable value in the diagnosis of acute brucellosis, but these procedures are notoriously inadequate as diagnostic aids in cases of chronic brucellosis. A positive agglutination test, particularly of low titer, and a positive skin test do not indicate that the person is suffering from brucellosis at the time the tests are made. Both the agglutination test and the skin test will yield entirely negative results in an appreciable number of persons from whose blood *Brucella* may be recovered.

4 In our hands, the opsonocytophagic test has yielded a high proportion of inconsistent results. We have found this test to be of little or no value as a diagnostic procedure or as a guide to therapeutic response.

5 Since it is now well-established that brucellosis is caused most frequently in this region by the ingestion of raw milk containing *Brucella*, the most important consideration in the control of the disease is adequate, controlled pasteurization of all milk and dairy products.

6 *Brucella* vaccine therapy has produced favorable results in from 60 to 85 per cent of patients with either acute or chronic brucellosis. Sulfanilamide and other sulfonamide drugs are apparently of little benefit. Artificial fever therapy has yielded favorable results, particularly in those refractory patients who do not respond to vaccine therapy.

DENTAL FOCI OF INFECTION*

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My experience as a pathologist and a teacher of both general and dental pathology influenced the selection of, and limitation of this subject to, "Dental Foci of Infection" What can be said that will be helpful in your evaluation of suspect dental lesions?

The problem of physician, dentist, or both is essentially one of diagnosis Proper appraisal of the history, physical findings and accessories or aids is the only satisfactory method Many failures, which should not be failures, result from too much attention to accessories The history is more or less neglected and the clinical examination slighted Appreciation of the time factor should be the greatest help and in those cases suspected of dental foci, knowledge of this time element will often be a most valuable link in the diagnostic chain

The concept of infection seems to have strayed from the narrow path of its original meaning It depends on the struggle between the invading agent and the defending host¹ First, the pathogenic organism must exhibit the ability to gain access, survive and multiply, second, it is opposed by the defensive mechanism of the body which includes immunological processes and tissue changes The latter is the primary concern of a pathologist

The importance of the oral cavity as a portal of entrance and a breeding place for microorganisms is apparent When the anatomy and physiology of the teeth, their supporting structures, the gingivae and alveolus are considered, they offer a constant nidus for the entrance and propagation of infection This was recognized by several investigators William Hunter,^{2, 3, 4} in his "Oral Sepsis as a Cause of Systemic Disease," did much to disseminate this idea

The overemphasis of laboratory aids or accessories, to the neglect of history and clinical findings, calls for comparison and evaluation, especially for bacteriology and x-ray

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BACTERIOLOGY

The literature on bacteriological investigation of dental foci of infection concerns three groups of bacteria. The first includes the fusiform bacilli and spirochetes or Vincent's organisms. Although there is increasing evidence that fusospirochetosis may cause systemic disease,^{5, 6} the other two groups are of more concern now. The second contains mainly the *B. acidophilus* group. Though the etiology of caries is not fully understood, there are two schools of thought. One emphasizes the internal mechanism and nutrition of the tooth, and the other advocates the external or bacteriological and chemical processes. By the fermentation of carbohydrates, these organisms produce organic acids and enzymes active in cavity formation. The dissolution of enamel and dentine or cement leads to involvement of the pulp, and a direct circulatory route for the entrance of bacteria through the apical foramen. This is the portal of entry for the third group, in which the chief offender is the *Streptococcus viridans*.

DEMONSTRATION OF BACTERIA

Bacteria have been demonstrated in many ways and in various sites. Smears, cultures, and animal inoculation have been used to isolate and identify organisms. Tissue stains have aided in both biopsy and post-mortem material. Periapical tissues, pyorrheic pockets, saliva, carious enamel and dentine, pulp, pulp stones and periapical bone have yielded various positive findings. Microorganisms have been found in blood, joints, heart, kidney, gastrointestinal tract, muscle, prostate, eye, nose, throat, bone, feces and urine which were considered to have their origin from dental foci. However, bacteria can be active long before they produce histopathological tissue changes or x-ray evidence of their presence.

BLOOD CULTURES

Recent investigations can be presented succinctly in two groups.

I. Occasionally positive blood cultures have been demonstrated in healthy individuals,⁷ temporary or transient bacteremias have been reported following operative procedures, dressing manipulations,⁸ urethral operations⁹ and tonsillectomies.^{10, 11} In 5,310 blood cultures on hospital cases Fox and Forrester¹² obtained their greatest percentage of

positives in subacute bacterial endocarditis (238 positive cultures)

II Immediately after extraction, positive blood cultures occur when previously the blood has been negative, and when in a relatively short time, the blood again becomes negative¹³ With periodontal disease the incidence of positive blood cultures after extraction may be even higher^{14,15} Rocking of teeth or massaging of the gingiva has been followed by positive bacteriemia^{15,16} Mastication of hard candy has been followed by temporary bacteriemia¹⁷ *Serratia marcescens* have been recovered from the blood following extraction, having been thus introduced into the gums¹⁸

The phenomenon, anachoresis, whereby certain foreign blood-borne substances, including bacteria, are attracted to and fixed in inflammatory areas, has a direct application to infected teeth Csernyei's experiments¹⁹ indicate that chronic periapical inflammations have an anachoric effect on microorganisms, and that organisms do not remain in the blood, but take refuge in the area of inflammation H B G Robinson and L R Boling²⁰ present the results of their experiments in which they were able to produce injury to the pulps of animals, following which they injected certain bacteria into the vein of a hind leg and later definitely recovered organisms from the site of injury

It has been demonstrated that bacteriemias (determined by positive blood cultures) may be transient, and in many instances be produced by artificial means or in extremely unusual circumstances Isolation of a bacterium from the blood stream gives neither its origin, nor tells what relation it has to systemic disease already present In practically all cases of subacute bacterial endocarditis, we incriminate the *Streptococcus viridans* In hospitals where repeated positive blood cultures have yielded a *Streptococcus viridans*, the patient ultimately proves to have either clinically, or at autopsy, endocarditis lenta Bacteriological evidences as to the type of organism about the tooth and supporting structures favor the green producing streptococcus However, is it not presumptuous to assume in most of these cases that the organism in the tooth, then in the blood and finally on the heart valve is necessarily the cause?

Finally, it is pertinent to evaluate bacteriological technique and reports Good technique is extremely difficult, time consuming and expensive Most of the work, to date, has been with aerobes Negative results do not always mean that organisms are not present, nor do positive findings always mean that such organisms are causal Special tests for viru-

lence and specificity, except in the hands of a few experienced workers, are rarely performed and need careful evaluation

X-RAY

X-ray examinations, when devoid of clinical data, should be regarded only as diagnostic aids or accessories. Compared with the knowledge of the presence of bacteria from a suspicious area, positive x-ray findings are more valuable. Assuming good standard technique, comparisons are based on radiolucent and radiopaque changes. Pathological changes may be present, and even good x-rays show nothing. On the other hand, the size of an x-ray area is not necessarily an index of the activity of a process. When changes are present in hard tissues, i.e., enamel, dentine and cement (the tooth proper) or the bone (the alveolus), the x-ray will be of greater aid than when changes are found in the soft tissue, where, however, sometimes by inference, conclusions may be justified.

As an index of dental infection, a radiolucent area is more indicative of activity than a radiopaque area. Changes have occurred to bring about a decrease in the harder tissue, a removal of the calcium. The most important cause of a radiolucent area is usually destruction, as (1) In caries due to actual loss of tooth substance, (2) when a root of a tooth has been removed, destroyed or resorbed, and (3) in bone with an abscess, granuloma or cyst, with sequestration in osteomyelitis, with a destructive tumor. Whether the infection is active or latent, and how little or how much it is contributing to a systemic infection is the main question. A single x-ray of a radiolucent area may be difficult or impossible to interpret. When however, successive x-rays reveal further progress and extension, associated with a history and clinical signs and symptoms suggesting a focus of infection, such evidence is strongly convincing.

In the light of infection radiopaque areas deserve less consideration. Increased density or condensation can be illustrated by (1) enamel nodules, (2) metallic fragments, (3) hypercementosis, (4) productive lesions, as osteogenesis, osteosis (exostosis), osteoma. As a result of infection, radiopaque areas do occur but in general they are best interpreted as bone scars and are testimony to the fact that healing has been adequate.

When successive x-rays originally reveal a radiolucent area, and

subsequently a change to more and more radiopacity, with a history and clinical symptoms and signs suggesting a dental focus, such evidence is quite convincing that the probability of such a lesion causing systemic manifestations is less and less

OTHER TESTS

The sedimentation test in dentistry, particularly with the present problem has received more attention of late^{21, 22} It is a laboratory aid or accessory which only exceptionally may indicate the activity of a dental focal infection When a series of successive tests are made for comparison, the information is much more valuable than with a single test, especially in interpretation of the progress of a condition

In dental literature an increasing number of claims for short wave diathermy have been made They are no doubt, a direct reflection of the popularity of this procedure in medicine

Benefits have been claimed not only from a therapeutic standpoint, but even as an aid in the diagnosis of dental infections—"Provocative irradiation"²³

Several have claimed that the application of "Short Wave" to a suspect dental focus, if active, will be followed by an increase in the sedimentation rate and that this test has considerable diagnostic value^{24, 25}

To elicit information on the vitality of a tooth, pulp testing is valuable While instruments may be employed for this, there are various clinical methods which are adequate in most cases

DENTAL FOCAL INFECTION

The crux of this situation is intimately related to a number of conditions frequent in dental practice It is to be regretted that in many of our medical schools they receive little or no attention Space will not permit as much consideration as they deserve Some of the more important conditions are briefly discussed

Caries, i.e., dental decay is the major problem of dentistry From such cavities, leading directly to pulp involvement, it may readily be appreciated how bacteria and infection can gain entrance (the most frequent pathway of entrance) to the pulp and the systemic circulation When evidences of infection are open, i.e., in direct communication with the outside world, drainage is more easily established and the dangers of systemic or distant involvement are less The lamina dura

when intact, indicates to many the absence of periapical infection

Periodontoclasia (pyorrhea) represents another major problem in dentistry. Many papers have been written on "pyorrhea" as a probable dental focus and this thought cannot be dismissed lightly. Three possibilities as to the *modus operandi* should be mentioned. Absorption of bacteria or their products directly into the systemic circulation from pockets, an exudation of purulent or infected material into the mouth and subsequent swallowing of such infected material, lastly, interference with mastication as the result of loose teeth. While the positive proof in support of any of these contentions is difficult, appreciation of the fact that most of the lesions in this condition are open lesions, at least diminishes the probability of absorption of bacteria or their products directly into the systemic circulation. This was one of the main contentions of William Hunter.²

In pyorrhea, the chief pathological features are alveolar resorption, pocket formation, loosening of the teeth with or without suppuration. Usually, calculus and evidences of infection in pockets are present.

Retained Roots Many statements concerning the danger of such roots are found. The cause of the root retention necessarily influences its danger. Information from the history, as to the probable cause and especially a knowledge of the length of time such retention has been present will be very helpful in evaluating such a focus. Where roots have been retained for years and the x-ray is negative or possibly shows condensation in contrast to a radiolucent area, less consideration as to the probability of an active focus of infection seems justified.

Dead Tooth When a tooth is traumatized severely so as to completely sever its periodontal attachment with obvious resultant death of the pulp (some reserve the term dead tooth for such a condition) this may or may not act as a dental focus. Usually, such injury will result in loss of the tooth within a short time after the accident. In such cases on account of open socket and free drainage if infection does occur the local defense will usually be adequate. In some cases, however, certain changes may usually be expected, resulting in resorption of the root and eventual loss of the tooth.

It cannot be denied that inadequate or unsatisfactory root canal therapy, sometimes the fault of the dentist, often the neglect of the patient, may be responsible for dental foci. As a result of recent encouraging advances especially in root canal therapy in prevention, diag-

nosis and treatment,^{26, 27, 28, 29, 30, 31} we are of the opinion that all pulpless teeth should not be needlessly sacrificed on the altar of focal infection.

Radicular—Granuloma—Cyst The next group is also frequent and important. As a rule they appear as more or less well localized radiolucent areas as a result of destruction. Their infectious nature cannot be denied. They are practically all associated with, or due to, devitalized teeth, sometimes a tooth which has had root canal therapy, but more often has not.

They are, in contrast to some of the others we have shown, closed lesions, they represent infection, possibly of a latent type, and are thereby a menace.

The more localized, the less the danger, but neither can it be denied that they are very frequently present without active local clinical evidences and in many individuals whose apparent health is excellent, and who remain so indefinitely.

Pulp stones are not uncommonly found in one or more vital teeth. While it is claimed they are of infectious origin,³² dental foci, or frequently the cause of neuralgia, the evidence appears more against than in favor. Dr. S. Sorrin, one of my associates on the Dental Service at Montefiore Hospital, advises me that in the dental examination of 200 cases of arthritis of various types (composed for the most part of cases of infectious arthritis) he found 100 were edentulous, 53 had less than 20 teeth and 47 had 20 teeth or more. In these 47, isolated pulp stones (4 teeth or less) were present in 15 patients.

While pulp stones may be composed of dentine or calcium, based upon an understanding of pathological changes in such conditions they are interpreted as degenerative rather than inflammatory.³³

Periosteal condensation, osteosis and osteoma It is not always easy to decide whether these changes are dystrophic, neoplastic or inflammatory. As said previously, in general, when of inflammatory or infectious origin, we interpret them as bone scarring and believe they represent evidence of a successful or adequate local defense.

SECONDARY MANIFESTATIONS

An extensive list of conditions has been attributed to dental foci. The organs involved include joints, muscle, nerves, kidney, heart, eye, gastrointestinal tract, nasopharynx and gall bladder. From this list there are three upon which to comment.

I The possible or probable relation of dental infection to heart disease is so extensive that comment will be made only on the relation of extractions to endocarditis. Recently, several reports^{34, 35} on subacute bacterial endocarditis developing within a short time after extraction of (infected) teeth have appeared. In a personal communication, I Salmon, Oral Surgeon and S. P. Schwartz, Cardiologist, of Montefiore Hospital reviewed 215 hospital cardiac cases of rheumatic, arteriosclerotic and syphilitic patients from whom a total of 1126 teeth had been extracted under local anesthesia. No cases of subacute bacterial endocarditis followed.

II, III Nasopharynx and Eye. More direct mechanisms and pathways of extension have been emphasized by several authors in affections of the antrum³⁶ and eye.³⁷ In striking contrast to the other parts of the body, the pathogenesis strongly indicates a direct extension or direct pressure on dental nerves rather than the usually accepted explanation of hematogenous spread.

By better medico-dental cooperation (and lately there have been encouraging evidences of it), greater progress can be made in the prevention, diagnosis and treatment of dental foci of infection. Sometimes, however, it is well to remember that although the ravages of infection may be incapable of repair, the progress of infection may be arrested and the source eradicated, if such cases cannot be improved, at least they should not be left otherwise.

Finally, lest I be misunderstood in my attitude toward bacteriology, let me paraphrase the words of Brutus, It is not that I love Bacteriology less but Pathology more.*

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LYMPHOGRANULOMA VENEREUM *

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LYMPHOGRANULOMA venereum is a widespread, contagious, venereal disease of human beings caused by a minute organism. The infective agent enters the body through the skin of the external genitalia without, however, always producing a demonstrable lesion at the portal of entry. It may also enter by way of the mucosa of the anal or rectal canals, and, much less frequently, by extragenital routes. The virus multiplies readily in the lymph nodes draining the affected areas, and probably, also, in the anal and rectal mucosae. It is transmissible to certain laboratory animals. The lesions of lymphogranuloma venereum are inflammatory in nature, subacute or chronic in quality of reaction, and are often marked by the development of multiple small foci of suppuration. Mortality is low. The disease is systemic with local manifestations appearing chiefly in the anorectal, inguinal and genital regions. It is customary, and convenient, to speak of the disease pictures in these areas as the anorectal, inguinal and genital varieties of lymphogranuloma venereum. There is, however, no evidence of the existence of any difference, other than regional, between the disease in the various sites.

Diagnosis of lymphogranuloma venereum is made, at present, by means of a skin test of a high degree of specificity and sensitivity which has been named after its discoverer, Wilhelm Frei.¹ Treatment of the disease with certain members of the sulfonamide series of drugs, notably sulfanilamide and sulfathiazole, has been very successful. The use of these drugs in the treatment of lymphogranuloma venereum has been of the highest value in that, prior to their introduction, there was no adequate remedy for the disease.

HISTORY

The inguinal variety of lymphogranuloma was the first of the manifestations of this disease to be suspected of being a separate clinical

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entity John Hunter² described, in 1786, a condition in which buboes developed without apparent cause, and were unaffected by mercury. Credit, however, for the earliest definite description belongs to William Wallace³ who, under the title of "indolent primary syphilitic bubo," gave an accurate description of what would now be regarded as a chronic suppurative case of the inguinal variety of the disease.

H. G. Klotz⁴ first called attention to the disease in this country. He reported having seen, in New York City, between the years 1879 and 1889, over 120 cases of a clinical entity which can hardly have been other than the inguinal variety of lymphogranuloma.

Durand, Nicolas and Favre,⁵ in 1913, gave the best clinical and pathological study hitherto published of the inguinal disease. They believed, erroneously, that the histological picture of lymphogranuloma resembled that of Hodgkin's disease, or lymphogranulomatosis, and proposed the term lymphogranuloma inguinale for the disease. The clinical and pathological manifestations of lymphogranuloma, however, are not peculiar to the disease and accurate identification was not possible until the introduction of the Frei test in 1925. Study and knowledge of the disease have progressed rapidly following Frei's important discovery.

In 1928, using the recently developed skin test, Frei and Koppel⁶ showed that a positive reaction was given by persons presenting inflammatory stricture of the rectum. Experimental proof of the lymphogranulomatous etiology of this condition was established in 1932 by Ravaut, Levaditi, Lambling and Cachera⁷ and Laederich, Levaditi, Mamou and Beauchesne⁸ who isolated a strain of the virus of lymphogranuloma venereum from inflamed rectal tissue. Mocquot, Levaditi and Reimié,⁹ in 1935, isolated from an inflammatory condition of the colon a strain of the virus with which Levaditi, Mollaret and Reimié,¹⁰ in the same year, produced the pathological changes characteristic of lymphogranuloma in the rectum of chimpanzees by direct inoculation into the mucosa.

The etiological agent of lymphogranuloma venereum was shown to be a virus in 1930 by Hellerstrom and Wassén¹¹ who inoculated *Macacus rhesus* and *Macacus cynomolgus* monkeys intracerebrally with suspensions of infected human lymph node. Two years later, Levaditi, Ravaut and Schoen¹² reported the transmission of the disease to mice by the intracerebral route. The mouse has since proved to be a very valuable animal in the study of lymphogranuloma. Strains of the virus have

TABLE I

NEW CASES OF LYMPHOGRANULOMA VENEREUM AND TOTAL NEW IN- AND OUT-PATIENT ADMISSIONS, NEW YORK HOSPITAL, 1934-40

Year	No of new cases of L V	Total No of new admissions	Cases of L V per 10,000 admissions
1934	26	43419	60
1935	23	44123	52
1936	31	45977	67
1937	35	44484	79
1938	35	43411	81
1939	28	41895	67
1940 (9 months)	34	31447	108

been maintained by successive mouse passage over a period of years and the infected brain has provided useful material, both as a source of virus for experimental purposes and for the performance of the Frei test. The etiological agent of lymphogranuloma was undoubtedly first seen by Gay Prieto¹³ in 1927 in the form of small cytoplasmic granules in material obtained from infected inguinal nodes. The granules were one micron or less in diameter and appeared frequently in small aggregations. They were also described, and figured, by Findlay¹⁴ who suggested the possibility that they represented the virus. Granules, however, appear sparsely in preparations of animal and human tissue, a fact which made it impossible until recently to procure active suspensions of the virus free from a large proportion of inert material. The work of Rake¹⁵ and his colleagues, who employed the yolk-sac technique of Cox,¹⁶ has now afforded a means of obtaining rich suspensions of granules. Successive passage of lymphogranulomatous material in tissue culture was observed by Sanders¹⁷ to increase the potency of the virus as high as one thousand times.

STATISTICS OF THE FREQUENCY OF OCCURRENCE OF LYMPHOGRANULOMA VENEREUM

Lymphogranuloma has been studied at the New York Hospital for the past eight years, for most of the time in a clinic specially devoted to

TABLE II

DISTRIBUTION, BY VARIETIES, OF 242 CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM IN 218 INDIVIDUALS

Variety	No of manifestations	Per cent
Anorectal	145	59.9
Inguinal	60	24.8
Genital	28	11.7
Asymptomatic	6	2.5
Miscellaneous*	8	1.1

* Includes one case each of carcinoma of rectum, cystitis, and granulomatous pelvic masses

the purpose. Close cooperation with all of the departments of the hospital has enabled every case of the disease found in the institution to be examined and treated. Table I shows the number of new cases seen annually since 1934, as well as the ratio of these cases to the total annual in- and out-patient new admissions. It will be seen that the proportion of cases of lymphogranuloma is increasing in the community from which the New York Hospital draws its clientèle. A further analysis of the material has revealed the increase to occur equally among all the varieties of the disease.

The local manifestations of lymphogranuloma constitute the most striking element in the clinical picture and occur, in order of frequency, in the anorectal, inguinal and genital regions. Table II shows that the anorectal is approximately two and one half times as common as the inguinal and about five times as frequent as the genital variety. The most frequently occurring combinations of varieties are the genital and inguinal and, less commonly, the anorectal and inguinal.

A small proportion of individuals give positive Frei reactions without any evidence of an existing, or preceding, infection with lymphogranuloma. Such people are usually detected in the performance of surveys of the incidence of the disease in a community, or during investigation of the contacts of an infected person.

Clinical manifestations of the disease, which do not fall into one of the three main varieties, represent about one per cent of the cases and,

in our material, are composed of, respectively, carcinoma of the rectum, cystitis, and granulomatous pelvic masses

THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

In conformity with all of the manifestations of the disease, the anorectal variety is acquired chiefly by sexual contact. Evidence which has been presented elsewhere, by the author and Henry,¹⁸ has shown that most cases of this variety, in males, arise by the direct implantation of the virus upon the anal or rectal mucosae, through the practice of sodomy. Infection of the lower bowel has also been acquired, in adults and in children of both sexes, by the use of an enema tip in common with a person suffering from the anorectal variety of the disease. It is clear, therefore, that the mucosa of the lowest portion of the human bowel provides an excellent medium for the growth of the virus of lymphogranuloma venereum. Experimental evidence has shown this to be true for the chimpanzee.¹⁰ The mode of acquisition of the anorectal disease by women has been the subject of much discussion. One school, represented by Bensaude and Lambling¹⁹ in France, is of the opinion that owing to the intimate connection between the vaginal and perirectal tissues, the disease begins in the latter tissues and spreads through the rectal wall into the mucosa. In support, it was claimed that of eighty women with rectal stricture, only twelve showed accompanying active inflammation of the rectal mucosa. These authors said, in effect, that if a case of anorectal lymphogranuloma showed stricture and proctitis, it could be assumed that the disease began in the rectal mucosa. If, however, there were stricture alone, the condition probably began outside the rectal wall and traveled through to the mucosa.

Examination of our material on this subject reveals that of sixty-seven women with stricture, no less than sixty-two, or 92.5 per cent, had an accompanying proctitis. By Bensaude and Lambling's own criterion, therefore, practically all anorectal infection with lymphogranuloma in women begins upon the mucosal surface and not outside the bowel wall. I am of the opinion that, in women, the virus, deposited during the sexual act by the infected partner, is enabled through the moisture of the parts to find its way to the anorectal mucosa and there to flourish, as in the case of the male. I am prepared to concede to Bensaude and Lambling the existence of some cases of anorectal lymphogranuloma which begin in the outer coat of the bowel. The clinical

TABLE III

ANALYSIS OF 145 CLINICAL MANIFESTATIONS OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Number	Per Cent
Stricture with proctitis	107	73.8
Stricture without proctitis	7	4.8
Proctitis without stricture	14	9.7
Esthiomène with stricture and proctitis	3	2.0
Fistula-in-ano	8	5.4
Perirectal abscess	2	1.4
Scarring of perianal tissues	1	0.7
Rectovaginal fistula	1	0.7
Elephantiasis of female genitalia with stricture	1	0.7
Elephantiasis of male genitalia with stricture and proctitis	1	0.7

TABLE IV

RACE AND SEX DISTRIBUTION OF 128 CASES OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Total cases	Per cent			
		White male	White female	Black male	Black female
Stricture with proctitis	107	38.3	15.0	3.7	43.0
Stricture without proctitis	7	28.6	14.3	0.0	57.1
Proctitis without stricture	14	71.4	7.1	21.5	0.0

condition in such cases is probably stricture without proctitis, of which we have only seen seven cases, two in men and five in women.

The clinical manifestations which are included in the anorectal variety of lymphogranuloma are chiefly the three entities of stricture with proctitis, stricture without proctitis and proctitis without stricture. These comprise over 88 per cent of the variety. The frequency of their distribution by race and sex is shown in Table IV where the comparatively high proportion of cases in white males should be noted.

I believe that proctitis without stricture represents the earliest objective sign of anorectal lymphogranuloma, and that, untreated, the great majority of such cases proceed to the development of stricture while the proctitis is still active. Of fourteen cases of proctitis without stricture I have only observed one to heal spontaneously, and that in a white man. Thirteen of the fourteen individuals were male homosexuals who adopted the passive role. Consideration of the history of their infection indicated that an average period of six weeks elapsed between infection of the rectal mucosa and the development of symptoms.

It should be the endeavor of all persons interested in the study of lymphogranuloma venereum to detect cases of the anorectal variety in the "proctitis without stricture" stage. Complete and rapid cure can then be obtained in over 75 per cent of cases. It is more difficult to heal a proctitis after the development of stricture. Little more than one-tenth of our cases of proctitis were observed before stricture had developed.

The earliest symptom of proctitis is the passage of blood and pus per anum. This is a direct consequence of the replacement of a portion of the anorectal mucosa by granulation tissue. Untreated, the granulomatous process extends deeper into the bowel wall, beginning usually at the posterior aspect and ultimately encircles the lumen. In the majority of cases, the replacement of granulation tissue by fibrous tissue begins to be evident, as a narrowing of the anal or rectal canals, less than three months after the onset of proctitis. In untreated cases, narrowing is slowly progressive.

I have only been able to observe closely three untreated persons during progression from early infection to complete closure of the bowel. In two of these the gamut of the disease was run in six, and in the third, in seven years. The number of cases, however, in which colostomy is required for relief of obstruction is relatively few, only nineteen persons out of a total of 128, or 14.8 per cent, having had to submit to this operation.

A question may be raised at this point as to the proportion of cases of stricture with proctitis, stricture without proctitis and proctitis without stricture which are lymphogranulomatous in origin. The question is answered in Table V in which it is assumed that clinical conditions may be regarded as lymphogranulomatous when the Frei reaction is positive, and non-lymphogranulomatous when it is negative. Accordingly,

TABLE V
THE FREI REACTION IN CERTAIN CLINICAL CONDITIONS

Clinical condition	Number of Cases			Per cent Frei- positive
	Frei- positive	Frei- negative	Total	
Stricture with proctitis	107	3	110	97.3
Stricture without proctitis	7	3	10	70.0
Proctitis without stricture	14	8	22	63.6
Fistula-in-ano	8	17	25	32.0
Perirectal abscess	2	8	10	20.0
Ulcerative colitis	0	29	29	0.0
Regional ileitis	0	3	3	0.0

97 per cent of cases of stricture with proctitis, 70 per cent of cases of stricture without proctitis and 63 per cent of cases of proctitis without stricture are due to the virus of lymphogranuloma

In view of the readiness with which the virus produces lesions in the lower bowel, our material was further studied to determine the extent to which the Frei reaction is positive in acute and chronic ulcerative colitis and in regional ileitis. No positive reaction was obtained in twenty-nine persons with ulcerative colitis or in three with regional ileitis. It may, therefore, be assumed that the virus of lymphogranuloma venereum does not often play a demonstrable part in the etiology of these two conditions. Our results with ulcerative colitis are in keeping with the experience of Rodaniche, Kirsner and Palmer²⁰ who reported that thirty-two of thirty-four patients with chronic ulcerative colitis had negative Frei reactions and showed no evidence of neutralizing antibodies in their sera against the virus of lymphogranuloma venereum. In regard to the two Frei-positive persons in their series, consideration was given to the possibility that the virus, although not directly responsible for the bowel ulceration, might have paved the way for other necrotizing agents to become established, as Frei originally suggested.

The remaining clinical manifestations of the anorectal variety of lymphogranuloma are shown in Table III. With the possible exception of esthiomène, which can be closely mimicked by granuloma venereum

TABLE VI

CLINICAL MANIFESTATIONS OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No of cases	Per cent
Suppurative adenitis, unilateral	34	56.7
Suppurative adenitis, bilateral	9	15.0
Non-suppurative adenitis, unilateral	14	23.3
Non-suppurative adenitis, bilateral	3	5.0

and which may occur without rectal involvement, the seven lowest entities in the table are by no means strictly of lymphogranulomatous origin. Further consideration of Table V shows that only about one-third of the cases of fistula-in-ano, and approximately one-fifth of those of perirectal abscess, are due to the virus of lymphogranuloma.

A word should be said about *esthiomène*, a term which, in the original Greek, meant eating or eroding. The disease is peculiar to women and the original description given by Huguier²¹ in 1849 is applicable today. He said, "This chronic malady is characterized by a leaden or violaceous tint of the parts. Deformity, ulceration and destruction may occur with concomitant hypertrophy and infiltration of such a nature that the orifices and canals which open into the vulvoanal region can be at the same time ulcerated, enlarged and strictured."

THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

The inguinal variety results from the deposition of the virus within the territory drained by the inguinal and femoral nodes. The actual site of invasion of the tissue—the primary lesion—is not often demonstrable. In sixty cases of this variety in our material, it was present in fourteen, or 23.3 per cent.

The virus is lymphotropic and produces clinical manifestations in the affected nodes 7 to 21 days after the infecting coitus. The nodes enlarge, sometimes to a considerable size, are painful, and the overlying skin is of a dusky red or purplish tint. In Table VI are shown the clinical manifestations of the inguinal variety in our material. In about four-fifths of the cases the disease is unilateral and in the remaining one-fifth,

TABLE VII

RACE AND SEX DISTRIBUTION OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Race and Sex	No of cases	Per cent
White male	39	65.0
White female	2	3.3
Black male	15	25.0
Black female	4	6.7

bilateral Frank pus appears in the nodes in approximately three-quarters of the infected persons and, in the absence of treatment, breaks through the overlying skin. The sinus thus formed may persist for months constantly draining seropurulent material. Many of the non-suppurative cases heal spontaneously.

The most striking element in the architecture of the diseased node is the presence of a large number of small foci of suppuration which are termed stellate abscesses.

The inguinal variety of lymphogranuloma venereum occurs rarely in women. In our series of sixty cases only six, or 10 per cent, were found in women (Table VII).

THE GENITAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Table VIII shows the frequency of occurrence in our material of the entities which comprise this condition. Primary lesions constituted 50 per cent of the genital manifestations. Satellite adenopathy was not always a concomitant of the primary lesion nor was such adenopathy always purulent. The common type of primary lesion is an oval vesicle on a slightly larger, non-indurated, erythematous base. It measures in the neighborhood of 6 millimeters in the longer diameter which is usually placed at right angles to the long axis of the penis. It does not produce subjective symptoms and is commonly found on the shaft or glans near the coronal sulcus. Primary lesions of the vesicular type generally disappear within 2 weeks without leaving a trace of their presence. Ulcerated primary lesions occur rarely, and when they do a concomitant chancroidal or syphilitic infection is sometimes found. Primary le-

TABLE VIII

CLINICAL MANIFESTATIONS OF 28 CASES OF THE GENITAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No of cases	Per cent
Primary lesion with adenitis	10	35.7
Primary lesion without adenitis	4	14.3
Esthiomène with and without rectal involvement	6	21.4
Elephantiasis of penis	5	17.8
Elephantiasis of labium majus	1	3.6
Abscess of vaginal wall	1	3.6
Periurethral abscess	1	3.6

sions of lymphogranuloma are infrequent in women, two only having been observed in our material, one on the labium majus and the other on a perianal tab

Esthiomène is the second in order of frequency of the genital lesions and has already been described. Elephantiasis of the male and female genitalia produced by the virus is indistinguishable clinically from that due to any of the other known causes of the condition. Elephantiasis of the penis may be produced by the lymphogranulomatous process itself or may follow extirpation of bilaterally involved nodes. Of five cases in our series, three were the sequel of radical surgery and two arose spontaneously.

PARINAUD'S CONJUNCTIVITIS

Curth²² recently reported the case of an individual who developed, in May 1932, a painless conjunctivitis of the right eye following perverted intercourse. The right preauricular and submaxillary nodes became swollen and tender. Treatment with ineffectual remedies was continued until 1933 when vision was lost in the affected eye. The condition was untreated for the next 5 years during which there was slow progression of the lesion. In November 1938, the right eye showed swelling and inflammation of both lids with considerable edema, especially of the lower lid, and some purulent conjunctival discharge. There was marked destruction of the inner surface of the lids. The right globe

TABLE IX

CLINICAL CONDITION OF 11 PERSONS FROM WHOM SEMEN WAS OBTAINED FOR TESTING FOR LYMPHOGRANULOMA VENEREUM

Case	Nature and duration of clinical condition
1	Active proctitis, 13 months
2	Active proctitis, 3¼ years
3	Active proctitis, 4 years
4	Active proctitis, 4½ years
5	Active proctitis, 6 years
6	Unhealed suppurative groin nodes, 10 days
7	Healing non-suppurative groin nodes, 3 weeks
8	Suppurative groin nodes, healed, 4 weeks
9	Suppurative groin nodes, healed, 16 months
10	Suppurative groin nodes, healed, 22 months
11	Unhealed primary penile lesion, 14 days

was intensely injected. The cornea was opaque. There was no longer enlargement of any of the lymph nodes. Experimental work by Curth and his colleagues established the lymphogranulomatous etiology of the conjunctivitis, thereby confirming the original observation of Levaditi, Bollack, Basch and Desvignes,²³ in 1936.

ASYMPTOMATIC CASES OF LYMPHOGRANULOMA VENEREUM

This group comprised three white men and three white women in all of whom there was neither existing evidence, nor past history, of infection with the virus. All, however, gave a positive Frei reaction. The marital partners of two men and one woman presented active lesions in the inguinal nodes, the anorectal mucosa and bladder wall respectively. Examination of the contacts of the other three persons was not possible.

Consideration of the group of asymptomatic cases leads to the question as to whether reservoirs of the virus exist other than in the discharges from the bowel and from the infected nodes. An attempt was made by the author to answer this query in 1935 by the examination of specimens of semen from eleven individuals who presented active or healed manifestations of lymphogranuloma. The nature of the lesions

which were presented by the group is shown in Table IX. The existence of virus in the semen was sought by diluting the material with an equal volume of physiologic saline, inactivating by heat, as in the preparation of Frei antigen, and injecting 0.1 cc intradermally into lymphogranulomatous subjects. In the presence of inactivated virus, positive Frei reactions would have followed this procedure. In no instance, however, was such a reaction obtained. It was therefore concluded that the virus of lymphogranuloma venereum is not present in measurable quantity in the semen and that infection is probably not transmitted by this secretion. The apparent lack of infectivity of semen suggests that lymphogranulomatous proctitis following sodomy arises from an open primary lesion in the active partner, or from an infection of his bladder mucosa.

THE SYSTEMIC MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM

The chief systemic manifestation of lymphogranuloma venereum is the hypersensitivity of the skin as a whole to the intradermal injection of suspensions of the inactivated virus. In the case of the inguinal variety of the disease, this develops at about the same time as the enlargement of the nodes and, in the anorectal variety, approximately one month after the appearance of the anal discharge.

Lymphogranuloma venereum may present a clinical picture of acute or chronic febrile illness in which local manifestations are present only in minor degree or may be entirely absent. Harrop²⁴ and his colleagues have recently reported such cases in workers in the virus, two of whom apparently acquired the infection through the respiratory passages. In one instance the sole localizing manifestation was a moderately enlarged supraclavicular node. In the other there were a greatly swollen uvula, non-suppurative cervical adenitis and recurrent bouts of pyrexia of moderate degree. A third person showed only malaise, fleeting muscular pains, and mild fever.

The inguinal variety of lymphogranuloma is usually ushered in with fever of short duration. Chills and joint pains may be present. The patient is seldom more than mildly ill.

Constitutional manifestations rarely accompany the onset of the anorectal variety. As the disease progresses, however, the individual presents the picture of chronic illness. Loss of weight appears most commonly and is accompanied by anorexia, insomnia and nervousness.

Symptoms of intestinal obstruction are much less frequent than the narrowing of the rectal lumen would lead one to expect. After the disease has persisted for several years, arthritis develops in about 10 per cent of the cases. The joints most commonly affected in our series were the wrists, fingers, elbows, ankles and knees in descending order of frequency. There is hydrops of the affected joint and erythema of the overlying skin. Aspirated synovial fluid is bacteriologically sterile and does not contain the virus. Joint destruction does not occur and full function is ultimately restored. Untreated arthritis waxes and wanes over a period of years and is sometimes of sufficient severity to require bed rest.

A systemic effect of lymphogranuloma reported by Gutman²⁵ is hyperproteinemia due to a large increase in serum globulin. It was found that, of seventy-two lymphogranulomatous persons in all stages of the disease, two-thirds had total serum proteins in excess of 80 per cent, the upper limit of normal, and approximately four-fifths had serum globulins in excess of 35 per cent. Marked hyperproteinemia occurred particularly in persons with chronic complications, notably in those with rectal stricture. Of forty-two such individuals over 80 per cent showed hyperproteinemia with values up to 114 per cent. Repeated determinations, made over periods of almost 2 years, indicated that the elevated serum protein values tend to persist for indefinite periods at an approximately constant level. The significance of hyperproteinemia in lymphogranuloma is as yet unknown.

THE VIRUS OF LYMPHOGRANULOMA VENEREUM

The etiological agent of lymphogranuloma is a virus which is filterable through Berkefeld V or Chamberland L 3 candles. It is transmissible to monkeys, mice, guinea pigs, cats, dogs and to certain rodents such as the field vole, the spermophile and the striped ground squirrel. The virus can be observed microscopically in the form of cytoplasmic granules in the lesions of lymphogranuloma venereum of man, in the brains of infected monkeys, in the brains and lungs of infected mice, in experimental buboes in guinea pigs, and in the chorioallantoic membrane and yolk sac of the developing chick embryo. The dimensions of the virus, as shown by filtration through graded collodion membranes, are similar to those of the vaccinia virus, namely 0.125 to 0.175 micron.

The pathogenicity of strains of the virus for experimental animals is

low and little increase in virulence follows successive passage in them and in the chorioallantoic membrane of the chick

The action of the virus can be inhibited by the use of sulfanilamide, sulfapyridine, sulfathiazole, ^{26, 27} and by other sulfonamide compounds ²⁷

THE DIAGNOSIS OF LYMPHOGRANULOMA VENEREUM

Owing to the lack of specificity of the histological lesions, accurate diagnosis of the disease is impossible by microscopic methods. None of the clinical manifestations are peculiar to lymphogranuloma, the most pathognomonic lesion being stricture with proctitis of which we have shown that 97 per cent of all cases are lymphogranulomatous (Table V). Detection of the virus in lesions requires highly trained personnel, considerable laboratory equipment, much time, and cannot always be carried out even in known cases of lymphogranuloma.

The cutaneous test discovered by Frei has proved to be highly specific and has been, until now, the sole means of accurate diagnosis. The test depends upon the fact that the skin of persons who have, or have had, lymphogranuloma is hypersensitive to the injection of the inactivated virus of the disease. Such hypersensitivity usually persists throughout the life of the individual. In one instance only, a laboratory infection in a worker, has the development and disappearance of this increased cutaneous reactivity been reported ²⁴

The test is performed by the intradermal inoculation of an emulsion containing the inactivated virus. The inoculum is known as Frei antigen and the resulting reaction as the Frei reaction. Frei reactions are read at the end of 48 or 72 hours after the performance of the test. The positive reaction appears as an erythematous area, the central portion of which is more indurated and may take the form of a papule, papulovesicle or papulo-pustule according to the intensity of the reaction. The size of the erythematous area is of no diagnostic significance. Exact measurement, however, must be made of the dimensions of the papule when the test is read. The reading is positive when the diameter of the papule is not less than 6 or 7 millimeters, the figure depending upon whether the antigen has been prepared from human or chick, or mouse material. About three-quarters of all positive Frei reactions show a papule whose diameter ranges from 7 to 10 millimeters, the remainder give reactions larger than 10 millimeters. The original Frei antigen was prepared from bacteriologically sterile pus obtained from an unbroken

lymphogranulomatous bubo The pus was diluted with approximately five times its volume of physiologic saline and the contained virus inactivated by heating at 60° C for two hours on one day and for one hour on the next This material, now called human Frei antigen, is still used but is unsatisfactory for the following reasons (1) it is difficult to be certain that the products of noxious agents other than the virus of lymphogranuloma are not present, (2) the supply of suitable pus is very limited, (3) the content of virus (and probably the virulence) varies considerably among different samples of pus, and (4) control material is unavailable

It was in order to provide an unlimited supply of antigen, free from the disadvantages of human material, that mouse brain antigen was introduced by the author and Suskind²⁸ in 1934 This material is approximately an 8 per cent suspension, in physiologic saline, of mouse brain infected with a passage strain of the virus and inactivated in the same manner as in the preparation of human antigen Mouse brain material has none of the drawbacks of human antigen and is a valuable diagnostic agent It is not, however, a perfect product In over three-quarters of the tests, mouse brain control gives non-specific reactions which are, nevertheless, distinguishable from positive reactions

The ideal antigen would appear to be an inactivated emulsion of the granules of the virus Such material has now been provided by Rake¹⁵ following the growth of the virus in the yolk-sac of the developing chick embryo The new antigen and control are practically water clear, and have been designated lygranum antigen and lygranum control respectively Tests of lygranum antigen²⁰ indicate that it is at least the equal of mouse brain antigen in sensitivity and specificity

Lygranum control is superior to mouse brain control in producing non-specific reactions in only 6 per cent of persons as compared with 78 per cent in the case of mouse material Such non-specific reactions are readily distinguished from positive reactions

It was stated above that the Frei cutaneous test was, until now, the sole means of accurate diagnosis of lymphogranuloma Within the past 2 months Rake³⁰ and his colleagues have employed lygranum antigen in a complement-fixation test The results obtained with the new test have been most striking In well over 90 per cent of sera there was complete agreement between the results of the cutaneous and complement-fixation tests³¹ My own impression is that the new test is at least

the equal of the Frei test in specificity and sensitivity. It has already established a special place in those instances where the cutaneous reaction is doubtful or negative, in the presence of clinical manifestations which could be regarded as lymphogranulomatous. The new test may also permit of a more delicate appraisal of the progress of the disease than is possible now when reliance must be placed entirely upon symptomatic change. It may not replace the cutaneous test for routine work in the field, for reasons of convenience of performance, but I believe that it will come to be regarded as the final court of appeal in determining the lymphogranulomatous status of a clinical condition.

THE TREATMENT OF LYMPHOGRANULOMA VENEREUM

Prior to 1938 treatment was carried on in our clinic by a variety of methods. These included injection of Frei antigen or antimony compounds such as tartar emetic or fuadin, aspiration, excision or incision and drainage of buboes, performance of colostomy with or without resection of the rectum, dilatation of rectal strictures, topical application of balsam of Peru to areas of ulceration on the external genitalia or anorectal regions, x-ray to the groin or rectum, medicated enemata and general supportive measures. None of these procedures afforded ideal treatment. The most satisfactory results followed the use of Frei antigen, by the subcutaneous or intravenous routes, but only a small proportion of the cases dealt with in this manner responded well.

In 1938 Gjurić³² reported good results in the treatment of twenty-three inguinal cases of lymphogranuloma by the use of a combination of fuadin and sulfanilamide. Shropshire³³ and Shaffer and Arnold,³⁴ in the same year, showed that the anorectal cases did unusually well following sulfanilamide therapy.

Between July 1938 and May 1940, thirty-one ambulatory cases showing various manifestations of lymphogranuloma were treated with sulfanilamide at the New York Hospital. The drug was given orally, usually commencing with 0.3 gm. to 0.6 gm. three times daily and increasing to 0.9 or 1.2 gm., three times daily. The exact dose depended upon the tolerance of the patient. Rest periods of 1 to 2 weeks were given on an average at 6 weekly intervals. In several cases, however, it was found necessary to discontinue the drug for a short time following 1 to 3 weeks' administration. Other patients, however, were able to take sulfanilamide continuously for 12 to 24 weeks without ill ef-

fects When changes in the blood picture occurred, the duration of the rest period was extended The average length of treatment, including rest periods, was, for the inguinal variety of the disease, 4 weeks, and for the anorectal, 29 weeks No other treatment was employed except aspiration of fluctuant buboes Of the inguinal cases 80 per cent were completely well within 3 to 6 weeks after beginning treatment and the remainder within 16 weeks An average total dose of 52 grams of the drug were required In the case of the anorectal variety, 39 per cent were completely healed within 9 to 79 weeks by the use of a total average dose of 172 grams of sulfanilamide Improvement to a marked degree occurred in another 39 per cent and no less than 92 per cent of all the anorectal cases showed benefit from the treatment The maximum total amount of the drug given to any healed patient was 330 grams during a period of 39 weeks One individual, who did not respond at all to treatment, received 584 grams of sulfanilamide in 53 weeks Untoward reactions, all minor in degree, occurred in 57 per cent of the individuals treated, and consisted of dizziness, headache, nausea and secondary anemia There was no demonstrable relationship between the sulfanilamide content of the blood and the ultimate therapeutic effect of the drug

Symptomatic relief coincided with the improvement in the proctoscopic appearance of the anorectal lesions, which began on an average 5 weeks after starting treatment The passage of mucopurulent and bloody stools gradually diminished and finally ceased altogether, rectal, perianal or abdominal pain subsided, difficulty with bowel movements vanished and a feeling of well-being returned accompanied by a gain in weight and the disappearance of systemic manifestations including arthralgia and myalgia Fibrous stricture of the rectum was not affected by sulfanilamide

Frei tests were performed upon a number of persons in the group, before and after sulfanilamide therapy No significant change in the degree of cutaneous reactivity resulted from the treatment.

Since May 1940 sulfathiazole has replaced sulfanilamide in the treatment of lymphogranuloma in our clinic The dose employed has been 15 grams three times daily for 2 weeks, then 10 gram three times daily for the next 3 weeks A rest period occupies the succeeding 3 weeks after which treatment is resumed, beginning with 15 grams three times daily as above Inguinal cases of the disease do not usually require a

second five-week course of therapy. Results, to date, show a slightly more rapid response to sulfathiazole than was found with sulfanilamide. This may be due to the fact that the amount of sulfathiazole administered in a given time to any patient, has been almost double that previously employed in the case of sulfanilamide. No toxic manifestations have yet been observed with sulfathiazole.

The marked beneficial effect which has attended the use of sulfanilamide and sulfathiazole in the treatment of lymphogranuloma springs from the virostatic effect of these chemicals upon the etiological agent of the disease.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



SEPTEMBER 1941

SURGICAL AND NON-SURGICAL TREATMENT OF THE PROSTATE GLAND*

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INTRODUCTION

ONE out of every four men over the age of 70 years has some deviation from the normal as regards the anatomical structure of the prostate gland. This fact was established by the author in a series of 250 consecutive autopsies on males at Bellevue Hospital. In addition, the prostate is subject to attack by various organisms in youth and young manhood, adding to the general incidence of prostatic disease. In later years, adenomatous hypertrophy and carcinoma and other malignancies enter the picture. The prostate gland is, therefore, an organ of considerable importance from the pathological standpoint, and must be reckoned with at all ages after puberty—and, indeed, even before puberty because sarcoma of the prostate occurs at any age.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The prostate gland consists of five lobes—two lateral, a middle, an anterior and a posterior. There are two accessory structures: (1) the

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subcervical group of tubules, occurring under the mucosa at the vesical orifice, and (2) Homes' gland, located in the mucosa of the middle of the trigonum vesicae. The various lobes of the gland send their ducts (averaging 63 in number) to open into the posterior urethra.

In adult life, the prostate is normally about as large as an English walnut. Located at the neck of the bladder, in a particularly strategic position for causing obstruction, even slight disturbances in the prostate assume exaggerated proportions.

The only proved function of the prostate gland is the production of a chemical substance which dilutes the testicular and seminal vesicular secretions and separates and activates the spermatozoa. The formation of an internal secretion has not been proved.

INJURIES TO THE PROSTATE GLAND

The prostate is well protected, but may be injured by external violence with fracture of the symphysis. More common are operative injuries and internal traumatism resulting from instrumentation.

DISEASES OF THE PROSTATE GLAND

PROSTATITIS

Prostatitis is a very common disease. It is usually associated with inflammation of the posterior urethra, seminal vesicles, vesical neck, trigone, or even the epididymes, and should, therefore, be studied in relation to both the urinary and genital tracts.

1 ACUTE PROSTATITIS

Etiology and Bacteriology. The most frequent cause of acute prostatitis is gonococcal infection. Non-specific acute infections are also common and have of late received much study. The organisms most often responsible are the *Staphylococcus albus* and *aureus*, *Streptococcus pyogenes*, and colon bacillus, but the *Bacillus proteus*, diphtheroid types, or other organisms may be present. Mixed infections are frequent. Contributing causes of prostatitis are masturbation over a protracted period, excessive sexual excitation without gratification, excessive sexual intercourse, and coitus interruptus.

Infection may reach the prostate by direct extension from the posterior urethra up the prostatic ducts (the most common way), or it may be descending, and secondary to an acute infection of the kidney or

bladder, or blood-borne, from a primary focus in the sinuses, teeth, or tonsils, or a complication of a systemic infection, such as influenza. A chronic prostatitis may be exacerbated into an acute condition by unwise instrumentation and manipulation in the treatment of chronic posterior urethritis and prostatitis.

Pathology Three types of acute prostatitis are recognized (1) acute catarrhal inflammation, which is always present in acute posterior urethritis and is usually caused by direct migration of the organisms up the prostatic tubules, (2) follicular prostatitis, which follows the first type and is characterized by many small abscesses and distention of the tubules with pus, which is not evacuated because of obstruction of the ducts, (3) parenchymatous prostatitis, an intensification of the second stage, the suppurative foci involving a greater extent of the surrounding stroma.

The termination of acute prostatitis is resolution, the formation of a large prostatic abscess, or chronic prostatitis.

Symptoms The onset of acute prostatitis may be mild, with few or no local symptoms, or it may be very severe. When of urethral origin, the initial symptoms are usually disturbances of urination—urgency, frequency, burning, pain during urination, dribbling. The prostate may enlarge to the point of causing complete retention, requiring catheterization. In acute prostatitis of hematogenous origin, the attack may be ushered in by a chill or fever, and there may or may not be urinary symptoms. Pain may vary from a sense of fullness in the perineum or rectum to acute pain—in the perineum, rectum, loins, penis, or above the pubes. There is leukocytosis.

Diagnosis Mild prostatitis is likely to escape observation during the course of acute gonorrhea. In severe cases, rectal palpation of a symmetrically enlarged, hot, tender gland is sufficient, with the symptoms and the findings of the two-glass urine test, to establish a diagnosis.

Treatment Treatment of acute prostatitis is expectant, and consists in absolute rest in bed for all febrile cases, avoidance of physical strain and sexual excitation, avoidance of trauma to the gland, the application of heat in the form of hot sitz baths, hot rectal irrigations, or diathermy, sedatives and belladonna and opium suppositories for pain, alkalization of the urine, and forced fluids if there is no urinary retention. With acute retention, catheterization may be necessary. Massage of the prostate and urethral instrumentation are contraindicated in the acute stage.

In addition to the above methods for symptomatic relief, chemotherapy has proved of great value in shortening the acute stage of prostatic infections. Sulfanilamide is a most useful drug in combating both gonococcal and non-specific infections. In bacillary infections, mandelic acid, and methenamine and sodium acid phosphate, are valuable.

2 CHRONIC PROSTATITIS

Chronic inflammation of the prostate gland is a very common condition in adult males. In our series of 350 postmortem studies, a large number of the specimens showed evidence of inflammation of the prostate.

The chronically infected prostate is a common focus of infection, and urologists have repeatedly emphasized the importance of examining the gland and its secretion when searching for the source of obscure infectious conditions. We regard the prostate as second only to infected tonsils as a cause of arthritis. It may also be responsible for endocarditis, neuritis, iritis, and myositis.

Etiology and Bacteriology Chronic prostatitis may result from any cause which congests the gland, such as long-standing infection, sexual abuse, or instrumental or other trauma. Other possible etiological factors are prostatic calculosis, stricture of the urethra, and certain vitamin deficiencies and endocrine dyscrasias.

Chronic prostatitis is most frequently the sequel to an acute infection, which may be caused by either the gonococcus or other organisms. The incidence of acute prostatitis as a complication of gonorrheal urethritis has been variously estimated at from 50 to 90 per cent, and untreated acute gonorrheal prostatitis, or incompletely treated posterior urethritis, is undoubtedly the most important factor in the production of chronic prostatitis. Only immediately after the acute inflammation has subsided is the gonococcus to be found in the prostatic strippings.

Chronic inflammations are by no means always due to the gonococcus, however. Non-specific infection is common, and may be a direct extension from the urethra, or blood-borne from a focus in the tonsils, teeth, or sinuses, or the aftermath of an acute systemic infection. The most common organisms demonstrated are the colon bacillus and the staphylococcus, streptococcus and their subforms.

Pathology Microscopically, there are usually to be observed regions of inflammatory reaction in and about the acini, characterized by an

increase of the polymorphonuclear cells, lymphocytes, and plasma cells, with marked proliferation of connective tissue. In other cases, the micro-pathological changes consist in circumscribed areas of round cell or polymorphonuclear cell infiltration. Minute abscesses are sometimes observed.

In a large percentage of cases, cystoscopic examination will show pathological changes in the region of the bladder neck, trigone, or posterior urethra. There is usually more or less involvement of the seminal vesicles, which may be soft and atrophic, or enlarged and indurated.

Symptoms The signs and symptoms of chronic prostatitis vary greatly. The most frequent complaints are of pain, a urethral discharge, which may be profuse or merely the so-called "morning drop," and some disturbance of sexual function, always accompanied by neurasthenia. The pain may be local or referred. Ordinarily, it is located in the perineum, and may be described by the patient simply as a "heaviness" in the rectum. With this type there is generally a history of the passage of prostatic fluid on defecation. The pain may be referred down the back or inner sides of the legs, or into the groins, penis, or sacrum, or it may simulate that produced by renal or ureteral stone. Frequent and painful urination, urgency, and difficulty are all common complaints, and result largely from involvement of the posterior urethra and bladder neck. If abscess occurs in the course of a chronic prostatitis, which is not uncommon with pyogenic infections, there is increased leukocytosis and pain, chills, and a rise in temperature.

Frequently the predominant symptoms are metastatic, with absence of local symptoms, so that the prostate is not suspected.

Diagnosis The diagnosis of chronic prostatitis should be based on (1) rectal palpation, (2) repeated analyses of the voided urine, (3) microscopic examination of the prostatic secretion and ejaculate, and (4) urethroscopic examination of the posterior urethra and vesical neck. It is often wise to delay this last procedure until the most distressing symptoms have been allayed by treatment.

Rectal palpation, though of the greatest importance, is not of itself sufficient to establish the diagnosis of chronic prostatitis since, not infrequently, palpation of the chronically inflamed gland may reveal no gross changes, yet pus cells will be found in the prostatic strippings. Many a prostate that feels normal functions poorly and contains large

amounts of pus and debris, and many microorganisms

Often, however, careful rectal palpation will reveal changes in and about the gland. It will be hard and nodulated, and usually adhesions can be felt extending from its lateral borders to the seminal vesicles and adjacent pelvic tissues. Such a prostate is ordinarily, but not always, enlarged, and sometimes there are boggy spots between the areas of induration. Areas of normal gland are usually present.

Microscopic examination of the prostatic fluid, expressed by massage, is the only reliable method of demonstrating the presence of infection in the gland. Often the diagnosis must rest solely on microscopic evidence of pus in the expressed secretions. In treating a case of chronic prostatitis, frequent microscopic examinations of the unstained prostatic fluid should be made, as the conditions present in the gland can be ascertained in this way much more accurately than by palpation. Negative findings on one examination of prostatic secretion are, however, insufficient proof of the absence of prostatitis, since pus in some instances does not make its appearance until after the prostate has been massaged from two to five times. The secretion expressed from the first massage may be from normal portions of the gland, and two or more manipulations may be necessary to open a pathway into the urethra from a closed-off focus of infection. Massage for diagnostic purposes must, of course, be carried out firmly enough to express the secretions, but very gently and cautiously, otherwise, epididymitis may result. The prostatic fluid should be stained at least once to ascertain the presence or absence of bacteria, and their type. Bacteria are more readily identified on smear than in culture, but many of the more chronic cases fail to show bacteria either on smear or in culture.

To secure uncontaminated prostatic secretion the patient is first asked to void his urine, the penis and meatus are cleansed with green soap and water, and the anterior urethra irrigated with rivanol dextrose, acriflavine, or other antiseptic solution. The patient kneels on the table and a small endoscopic tube is inserted to a point beyond the external sphincter into the prostatic urethra. He then bends over and rests on his hands or elbows. The prostate is massaged firmly but gently and finally the prostatic urethra emptied by vigorous strokes down the middle depression of the prostate. The uncontaminated prostatic fluid is received in a sterile test-tube which the assistant holds at the end of the endoscope.

Normal prostatic fluid is opalescent and viscid, and microscopically is seen to consist of corpora amylacea, lecithin globules, columnar epithelia, and occasional hyaline globules. In chronic prostatitis, the prostatic secretion is less opalescent than the normal fluid, and the normal elements are replaced by pus cells and degenerated epithelial cells. The degree of infection is measured by the amount of pus in relation to the lecithin. In well-developed chronic prostatitis much of the lecithin content will be replaced by pus cells, often in clumps. As the condition improves, the pus cells diminish and the normal elements reappear. Bacteria may be present in great numbers.

Urethroscopic examination of the posterior urethra is advisable in cases where palpation of the prostate and vesicles, analysis of the voided urine, and microscopic examination of the secretions have proved inconclusive. The marked chronic inflammatory changes that may be revealed by such examination not infrequently are the only clue to a low-grade prostatitis and vesiculitis.

Prognosis The patient suffering from long-standing prostatitis is not easily cured and it is advisable so to inform him at the outset of treatment. Relief of symptoms by some form of therapy, especially urethral dilatation, massage, rectal heat, and chemotherapy, is possible in most cases, but reversion to a normal prostatic fluid is more difficult to obtain and requires complete removal of infectious foci and restitution of prostatic drainage.

Treatment In general, treatment consists of dilatation of the prostatic urethra, prostatic massage, urethrovesical irrigations and instillations, heat applied in the form of hot rectal irrigations, hot sitz baths, or diathermy, chemotherapy, and hyperpyrexia and vaccine therapy in selected cases.

The elimination of distant foci of infection, in the tonsils, teeth, sinuses, or colon, is of the greatest importance. In these cases, local measures are useful in relieving the symptoms, but are of little value in cure of the prostatitis, which is dependent upon removal of the primary focus.

The main problem in the treatment of chronic prostatitis is the restitution of free drainage, since retention favors infection. The most effective method of restoring the potency of prostatic and ejaculatory ducts is by a gradual, gentle, but thorough *dilatation of the prostatic urethra* to its maximal capacity. Urethral dilatation should precede mas-

sage of the partially or totally retentive gland since massage is beneficial only when drainage can take place through patent ducts. Active instrumentation is permissible in most cases at the time of the first consultation, the only clinical requirement being a clear first glass of urine. Dilatation is best carried out by means of sounds (passed upon a bladder partly filled with a mild antiseptic solution). Dilatation is carried on two or three times a week until the largest possible sound has been passed on at least three occasions and has remained tight, indicating that the maximal capacity of the urethra has been reached. The voided urine should be examined before each instrumentation, and treatment discontinued whenever the urine becomes cloudy. A mild urethritis may develop when the occluded ducts resume drainage and empty their infectious contents into the urethra. It may then be necessary to employ urinary antiseptics—sulfanilamide, mandelic acid, salol, or methenamine with acid sodium phosphate—their selection depending upon the nature of the infecting organism. Clinical proof of improved drainage can be obtained by a comparison of the amount and composition of the secretion before and after dilatation.

When satisfactory drainage of the diseased prostate has been restored, *digital massage* may be given once or twice a week upon a bladder partly filled with antiseptic solution. The aims of prostatic massage are (1) the gentle expression of the accumulated secretion, (2) a stimulation of the contraction of smooth muscle fibers, and (3) the stretching and final removal of marginal adhesions. The technique, as well as the results obtained, vary widely with different operators. The patient may stand with the body bent forward, as over the back of a chair, or be placed in the Sims' position, or he may rest upon his knees and elbows. The operator, with his gloved index finger in the rectum, exerts gentle pressure upon the lobes palpable from that position, using a downward stroking motion with the force directed toward the urethra, the object being to empty the prostatic acini of their purulent contents and to break up adhesions about the gland. Secretions later may be expressed from the ejaculatory ducts and the sinus pocularis by bringing the firmly pressing finger downward along the posterior urethra. Most patients with chronic prostatitis are benefited by intelligent application of prostatic massage, but too early, too vigorous, too frequent, or unduly prolonged massage may cause acute epididymitis or other unfavorable reactions. The degree of pressure is a matter of experience and is gov-

erned largely by the degree of inflammation present. As a rule, massage is carried out twice a week at first—the treatments tapering off, as the condition improves, until the patient is receiving massage once a week, then every ten days, semi-monthly, and finally once a month.

Hyperpyrexia and vaccines, serums, and injections of foreign proteins have a limited usefulness. *Hyperpyrexia* has been found highly beneficial in certain severe cases of gonorrhea and in the treatment of most gonococcal complications, but it is expensive, very uncomfortable, and attended with considerable risk. We have found *vaccines* very helpful in certain cases of arthritis where the infective focus was in the prostate, but in other cases their use has resulted in no appreciable benefit. *Intraprostatic injections* of antiseptic solutions have been recommended for recalcitrant pyogenic prostatitis, our experience has been that the benefits are not sufficient to offset the hazards of this method.

Chemotherapy has given a new hope in the treatment of chronic prostatitis, with the introduction of the sulfonamides and mandelic acid. Other useful drugs are salol and methenamine used with acid sodium phosphate. When prostatic pain is very severe, sedatives are often necessary. The barbiturates usually suffice, but occasionally it is necessary to give codeine, pantopon, or morphine. When there is pain in the region of the prostate, or during micturition, the patient should be given a soothing prescription, such as Kirwin's mixture:

Potassium citrate	Drams VI (24 cc)
Tinct Hyoscyami	Ounces I (30 cc)
Tinct Opii camphorata	Ounces I (30 cc)
Elix Saw palmetto et Santalwood	
q s ad	Ounces IV (120 cc)

Sig —Drams II (8 cc) q 4 hours

Spices and alcohol should be eliminated from the diet and constipation avoided. When there is marked vesical irritation, a restricted diet should be used, which limits meat, tea and coffee, and eliminates certain foods which are irritating to the bladder, such as asparagus, carrots, tomatoes, berries.

The application of heat to the inflamed prostate has definite therapeutic value. Relief may often be obtained by hot sitz baths, hot rectal irrigations, diathermy, or radiothermy. The Elliott treatment regulator, introduced through the rectum, is an effective method of applying dry heat directly to the prostate and adjacent structures.

Occasionally a prostate becomes so infected that no amount of treatment by these methods will effect a cure Total prostatectomy is then indicated

PROSTATIC ABSCESS

Etiology Abscess of the prostate gland may follow failure of an acute diffuse parenchymatous prostatitis to subside or to become chronic Multiple small abscesses in the stroma coalesce to form one large abscess A frequent cause is the gonococcus, but our own studies have shown that many other organisms may be present in abscess cavities in the prostate Prostatic abscess may result from improper instrumentation, or occur as a complication of systemic infection, or be secondary to superficial pyogenic infections, such as carbuncles, boils, and felons In the last event, the causative organism is the *Staphylococcus aureus*

Symptoms and Diagnosis The symptoms are pain in the perineum, chills, fever, and frequent and painful urination which may progress to complete retention Leukocytosis is present Chronic abscess may persist for weeks without producing local symptoms There are occasional cases of huge prostatic abscesses in which the only symptom is difficulty of urination, this is due to the type and lack of toxicity of the infecting organism

The diagnosis usually is not difficult By rectum, the prostate is felt to be enlarged, hot, tender, and often asymmetrical The presence of fluctuation is conclusive If no fluctuation is detected, a needle may be inserted into the suspected area and pus withdrawn, if present If neither fluctuation nor pus is noted, a cysto-urethrogram may be helpful

Prognosis and Treatment An untreated prostatic abscess may rupture into the urethra or rectum, or burrow into the perineum, bladder, or even the peritoneum, with dire results Abscesses which empty their entire contents into the urethra are likely to be of the follicular type, or at least not deeply seated in the parenchyma Spontaneous evacuation through the rectal wall is a surgical calamity

If proper drainage is instituted, convalescence is usually satisfactory, although every case must be followed by a period of observation and treatment to insure a normal gland

Evacuation of a prostatic abscess *through the posterior urethra* is the method of choice A perineal section is done, the finger introduced into the prostatic urethra, and the honey-combed interior cleaned out

so that no pockets remain. A tube is then introduced into the bladder, diverting the urine and conducting the pus out through the perineal wound.

Evacuation may also be accomplished *from outside the urethra*. The posterior surface of the prostate is exposed as in a Young perineal prostatectomy, the abscess incised, and a tube inserted into it and fixed in position. The transvesical route is occasionally employed, but our own experience with it has not been encouraging.

SYPHILIS OF THE PROSTATE GLAND

Syphilis of the prostate appears to be exceedingly rare. We have personally never encountered a case, and very few have been reported in the literature.

Symptoms and Diagnosis There is nothing pathognomonic either in the symptoms or the rectal findings. The chief symptom is perineal pain, usually aggravated by urination. Less common are hematuria, pain on defecation or coitus, urinary disturbances, and retention. Prostatic massage usually produces a more or less characteristic discharge. On rectal palpation the prostate will be found markedly irregular, enlarged, and sometimes nodular. The Wassermann test is usually positive.

Prostatic syphilis is a late manifestation of lues, and occurs, usually, between the ages of 40 and 65 years, when it may be very difficult to differentiate it from hypertrophy of the prostate and carcinoma.

Prognosis and Treatment If diagnosed early, the disease responds readily to antiluetic treatment, if unrecognized, the prostate may be destroyed by gummas.

Treatment consists of the usual antiluetic measures, reinforced by surgical drainage of necrotic gummas.

TUBERCULOSIS OF THE PROSTATE GLAND

Etiology and Incidence Tuberculosis of the prostate is a disease of the young adult and, as a rule, is observed in those in the third and fourth decades of life. It is almost always a secondary involvement in a progressive tuberculosis which is extending throughout the urogenital system. In most instances it is probably an extension from the seminal vesicles. Between 50 and 70 per cent of all cases of tuberculosis of the male genital tract show involvement of the prostate.

Pathology At first the prostatic lesion may be confined to the region

about the ejaculatory duct on the side corresponding to the infected vesicle, whence it spreads, by way of the acini or the lymphatics, to other parts of the gland. In the rare cases in which the prostate is infected by tubercle bacilli conveyed in the urine, the initial lesion is periurethral.

The first pathological change is the formation of tubercles. The tubercle bacilli are apparently first deposited in the walls of the small capillaries. Other tubercles develop from these original foci and extend in the usual manner. Later stages are fibrosis, caseation, and suppuration. Suppuration may result in rupture of an abscess through the prostatic capsule, with the formation of an intractable perineal fistula, or there may be rupture into the urethra. Spontaneous healing is rare. Small caseous areas may become encapsulated and latent, or they may undergo calcification and encapsulation.

Symptoms and Diagnosis With well-walled-off tubercles, there may be no untoward symptoms whatsoever. If the tubercles have coalesced and finally ruptured into the urethra, there will be frequency, dysuria, hematuria, and pyuria.

Rectal examination reveals a nodular, elastic gland, usually affected on one side only, and differing from a carcinomatous condition in that it lacks the board-like consistency usually associated with the latter. The secretion may show tubercle bacilli. Differential diagnosis is based chiefly on microscopic study of a specimen of diseased tissue.

Treatment The hygienic, dietary, and therapeutic measures advocated for postoperative and inoperable tuberculosis of the urogenital tract are usually prescribed, and good results have been obtained by us therefrom in some cases. When calcium deposits are present, total prostatectomy is indicated. On the other hand, in acute and subacute tuberculosis of the prostate, operation is distinctly contraindicated. Even in the presence of abscess, it is preferable to allow it to absorb or rupture into the urethra rather than to evacuate it through the perineum, as this is likely to result in a persistent fistula. Radical removal of the genital tract is inadvisable in patients with extensive involvement of the prostate gland.

CYSTS OF THE PROSTATE GLAND

Cysts of the prostate gland are decidedly rare. They may be either congenital or acquired. The most common is the simple retention cyst,

which may arise in any portion of the gland and is merely a normal acinus the duct of which has become occluded, causing expansion of the acinus

Treatment Smaller retention cysts, producing no symptoms, are best left alone. When treatment is necessary, destruction of the cyst by fulguration, or removal by prostatic resection instruments, is the treatment of choice.

PROSTATIC CALCULUS

Incidence and Etiology Prostatic calculi are relatively common. In an autopsical study of 250 prostates from subjects of all ages, I found one or more stones in approximately one-fifth of the glands.

Prostatic calculosis may occur at any period of life, but is rare before the age of 30 years. Of the twenty-three patients reported on by Lowsley and Hawes, only one was under 40 years of age.

Distinction must be made between (1) endogenous, or true prostatic calculi, namely, concretions formed within the prostatic substance, and (2) exogenous, or false calculi, which are urinary stones that have lodged in the prostatic urethra or have formed primarily from urinary sediments in a communicating pouch. The nucleus of a true prostatic stone is composed of organic material of an albuminoid nature: corpora amylacea, a blood clot, epithelial detritus, a clump of bacteria, or necrotic tissue from an abscess. The inorganic element forming the laminated layers about the nucleus is composed of inorganic salts.

The exact etiology of true prostatic stones is unknown. The most commonly held theory is that first advanced by Thompson in 1868, namely, that they have their origin in corpora amylacea, which, under certain conditions, act as foreign bodies and set up an inflammatory reaction in the mucous membrane of the acini enclosing them, as a result of which calcium phosphates and carbonates are cast off, these impregnate the corpora amylacea and convert them into calculi.

Pathology True prostatic calculi are usually multiple, small, rounded (without facets), and scattered indiscriminately throughout the parenchyma. Occasionally a cluster of stones will be found in one lobe while the remaining lobes are free of calculi. Sometimes there will be a single large stone, or one large stone in association with numerous smaller ones.

Microscopically, the portion of the gland containing the calculi

shows distended acini, the mucosal linings of which are infiltrated by lymphocytes or by polymorphonuclear leukocytes

Benign adenomatous hypertrophy and prostatic calculosis not infrequently occur together (18 of 23 cases, Lowsley and Hawes) The calculi are seldom, if ever, located within the adenoma, but are found between it and the capsule, embedded in the remnants of the true prostate Frequently, however, calculi-containing prostates show no sign of hypertrophy They may be senile and fibrotic, with atrophy of the parenchyma and evidence of inflammation

Symptoms and Diagnosis The most important symptoms are disturbances of urination, the actual passage of calculi either spontaneously or following massage, and localized or referred pain—in the perineum, suprapubic region, rectum, or down the penile shaft In many cases the symptoms are overshadowed by those of an associated hypertrophy or prostatitis In others, no symptoms are present, and the stones are discovered accidentally

It is frequently possible to make a presumptive diagnosis of prostatic calculi by the rectal palpation of a hard, circumscribed area suggestive of stone or a nodule, or by the eliciting of crepitation Urethroscopic examination may reveal the presence of stones in the prostatic ducts Positive diagnosis is made by roentgenography Cysto-urethrogramms are of value not only in revealing the calculi, but in determining the type and degree of obstruction to urination, and associated pathology, if present

Treatment Small calculi, that are discovered accidentally and give no subjective symptoms, are best left alone In older men, who have neared the end of sexual life, we prefer to treat prostatic calculosis by total prostatectomy, both when there is associated adenomatous hypertrophy and when there is no hypertrophy but infection and fibrosis are present Prostatotomy, transurethral resection, and even the usual conservative perineal or suprapubic prostatectomy often leave enough calculi or infected prostate to cause persistence or recurrence of symptoms, as has been repeatedly demonstrated by postoperative roentgenograms Younger men with numerous stones in their prostates should be treated by prostatectomy as a rule Transurethral resection is also frequently employed, but has the disadvantage that stones are often left behind in the prostate

SARCOMA OF THE PROSTATE

Sarcoma of the prostate is relatively rare, and may occur at any age. A review of the literature by Lowsley and Kimball, in 1934, disclosed only 132 reported cases, 35 of which occurred in patients under 22 years of age. These tumors usually grow rapidly and attain large size, early infiltrating the bladder, seminal vesicles, and rectum. Growth of the tumor backward beneath the base of the bladder pushes the latter upward and forward, causing obstruction of the ureteral orifices, urethral orifice, and urethra, with resultant partial or complete retention. Growth of the tumor toward the perineum causes prolapse of the rectum, with obstruction to defecation and urination.

Diagnosis Early diagnosis is essential. In early cases rectal examination may be negative, but usually reveals a palpable nodule. Occasionally the growth may be indurated and nodular, but usually it is of uniform consistency and has an elastic "balloon-like" feel, hence the condition may be erroneously diagnosed as abscess. The diagnosis can positively be made by needle biopsy.

Prognosis and Treatment The prognosis is poor. The most favorable results have been achieved through the use of radium and Roentgen rays. In early cases, the skilled use of these agents may prove curative, and in late cases they may give relief and prolong life. Operative intervention should be limited to the relief of obstruction and the treatment of complications.

CARCINOMA OF THE PROSTATE GLAND

Carcinoma of the prostate, because of its frequency and its essentially fatal nature, presents the urologist with his most baffling problem. Young's statistics (1935) reveal that a fifth of the male patients who seek relief of obstruction of the vesical neck have carcinoma of the prostate.

Pathology A striking morphologic peculiarity of carcinoma of the prostate gland, that has been emphasized by most authors, is the diversity of its forms. In the same case, in different portions, the carcinomatous proliferation may be found at one time as an adenocarcinoma and again as a scirrhus, a medullary, or a squamous-cell carcinoma.

A large percentage of prostatic carcinomas are associated with benign hypertrophy. In only 10 (13 per cent) of the 72 cases studied by Wilson and McGrath was there no evidence of associated hypertrophy.

CHART I
INCIDENCE, BY AGE-GROUPS, OF CARCINOMA IN RELATION TO BENIGN
ENLARGEMENT IN 280 CASES

Age of group	Prostates examined	Per cent showing carcinoma	Per cent showing benign enlargement	Per cent of carcinomas which arose in a prostate with benign enlargement	Per cent of benign enlargement which also showed carcinoma
31-40	28	0%	4% (1)	0%	0%
41-50	23	17% (4)	30% (7)	25%	14%
51-60	65	14% (9)	37% (24)	50%	21%
61-70	77	23% (18)	67% (52)	66%	23%
71-80	63	21% (13)	68% (43)	46%	14%
81-90	24	29% (7)	75% (18)	71%	27%

In his very complete study of 280 prostates from men between the ages of 31 and 90 years, Robert A. Moore found the occurrence of carcinoma and benign enlargement to be as shown in Chart I. It is evident, therefore, that the possibility of carcinoma must be kept in mind in every case of prostatic hypertrophy.

Numerous careful studies show that in over 75 per cent of cases the carcinoma starts in the posterior lobe (the portion of the gland which does not participate in benign adenomatous hypertrophy).

Prostatic carcinoma is, as a rule, insidious and slow-growing, though highly malignant, and may remain confined to the prostate and periprostatic region for long periods. Only 10 to 20 per cent, according to Barringer, are radiosensitive.

In many cases, by the time the growth has become sufficiently advanced to be clinically diagnosed, it has extended beyond the posterior lobe into the lateral and median lobes and upward to the base of the prostate. There it may penetrate the capsule and involve the seminal vesicles. Through the prostate's rich supply of lymphatics, the carcinoma may extend to the pelvic nodes, or, by the perirectal plexus, to the abdominal nodes. Dissemination through the blood stream may occur early, and distant metastases, particularly in the bones, are often detected before the occurrence of local symptoms. The small prostatic tumor often disseminates widely. The high frequency of skeletal metastases, and the predilection for the pelvis and lumbar vertebrae, have been noted by practically all observers.

Symptoms. The symptoms are not characteristic. Disturbances of urination are usually the first symptoms, but advanced carcinoma may

be present without urinary symptoms. Pain—referred to the sacroiliac region, rectum, perineum, or suprapubic area—is often an early symptom, and may be due to metastases to the bones. Terminal hematuria, retention, loss of weight and strength, and constipation are significant, but late, symptoms.

Diagnosis Carcinoma of the prostate has, unfortunately, usually existed for a long period by the time it is recognized. The diagnosis is based upon the findings of rectal palpation and microscopic examination of a biopsy specimen removed by means of an instrument, such as the Lowsley biopsy instrument. In well-advanced cases recognition is usually not difficult, but in early cases, in the soft (medullary) type of carcinoma, and in carcinoma superimposed upon a benign hypertrophy, diagnosis may be difficult. A single, small nodule may easily escape notice, especially when masked by edematous prostatic tissue or in the absence of symptoms. The entire gland may be irregularly enlarged, of a board-like hardness, and fixed, but usually the growth is in the form of a nodule or hardened area in the posterior lobe, where it is readily palpable by rectum. Evidence of the fixed gland may be seen on cystourethroscopic examination.

Prognosis and Treatment The prognosis in the past has been cheerless in the extreme. Over 95 per cent of the cases are beyond cure when first seen. The high early incidence of pelvic lymphadenopathy, capsular infiltration and invasion of the contiguous structures, and skeletal metastases precludes the successful surgical treatment of the disease in most cases.

In cases in which the carcinoma is confined to the prostate and periprostatic region, total or subtotal perineal prostatectomy yields a fair percentage of cures estimated upon a 3 to 5 years' basis, and prolongations of life for considerably longer periods are not uncommon. If seen too late for hope of radical removal, partial perineal prostatectomy, or transurethral resection of the obstruction, with implantation of radon seeds, is the method of choice.

Improvement in prognosis is dependent on an increase in the number of early diagnoses, with radical removal.

BENIGN HYPERTROPHY OF THE PROSTATE

Benign hypertrophy of the prostate gland occurs in from one-third to one-fifth of all men over 50 years of age.

Etiology Many theories have been advanced as to why the prostate tends to hypertrophy with age. The chief are (1) that the hypertrophy is due to true tumor formation, which takes its origin, according to some, from the periurethral accessory glands, or, according to others, from any part of the prostate gland proper, (2) that it is a fibroepithelial growth akin to myoma of the uterus, (3) that the condition is a cystic glandular hyperplasia having its basis in infection of long standing, (4) that the hyperplasia is endocrinopathic, and due to an improper balance between the male and female hormones.

Pathology Benign hypertrophy of the prostate most frequently occurs in the middle and lateral lobes—the anterior lobe being affected rarely, and the posterior lobe practically never. My studies show that the portion which enlarges most frequently is really a contiguous structure—the subcervical group of tubules. These may enlarge without hypertrophy of the prostate, but when the prostate proper is enlarged, the subcervical group will also be hypertrophied. If a portion of the gland protrudes into the bladder, it will usually be found to be the subcervical group of tubules.

Microscopically, four types of benign enlargement may be distinguished: glandular, cystic, fibroglandular, and fibrous. The much-discussed question as to whether adenomas or fibromyomas predominate in prostatic hypertrophy is of little practical importance as it is established that a pure formation of either type never occurs.

In prostatic hypertrophy there is a definite line of cleavage between the capsule and the prostatic tissue, making separation of the adenomatous prostate from the capsule an easy matter.

Symptoms Enlargement of the prostate is usually an insidious disease, which develops slowly and is marked by gradually increasing frequency and nocturia. The patient notices that the character of the stream changes—it is often slow in starting, and lacks force. Men take this as evidence of advancing age and often pay little attention to it. The condition gradually gets worse, and is usually accompanied by urinary infection. Often microscopic blood is present, and occasionally macroscopic hematuria. In the rare case, complete obstruction of urination may occur without any premonitory symptoms.

The urine usually contains pus, blood, and albumin. If the disease is of long standing, casts are found, and the phenolsulphonphthalein test will show diminished renal function. The blood urea is increased, some-

times very greatly, but unless there is fever, the blood count is usually within normal limits

Diagnosis The patient should be given a careful general and special examination, including rectal palpation, an estimation of the amount of residual urine, determination of the renal function, and a cystoscopic examination to ascertain the exact nature of the enlargement. The size of the prostate as felt by rectum has nothing to do with its obstructiveness, and cystoscopy, or cysto-urethrography, is essential to determine the extent of the intravesical and intraurethral intrusion.

Treatment Many patients with benign hypertrophy of the prostate have no obstructive symptoms and do not require surgery. In benign hypertrophy without residual urine, *palliative treatment* is usually advisable, this consists of periodic prostatic massage, urethral dilatations, urethrovessical irrigations, the application of heat to the prostate, and hydrotherapy. Periodic check-up is essential.

Hormonal therapy affords symptomatic relief in some early cases of prostatism with slight or moderate urinary disturbances, but even its most enthusiastic advocates do not claim that it benefits all types of cases, or that it is to be considered a substitute for surgical relief in major prostatic obstruction.

Roentgen therapy of benign hypertrophy also is an accepted procedure, but opinions vary as to the effect of such treatment. The more conservative urologists and radiotherapists incline to the opinion that the only effects of irradiation are a definite alleviation of the associated congestion and edema, giving temporary relief in selected cases. It cannot, however, be regarded as a substitute for prostatectomy or resection.

Surgical treatment is usually required in cases with residual urine. Every patient presents an individual problem, and the type of operation selected should be the one best suited to the case in question. It has always been our contention that every well-trained urological surgeon should be psychologically and technically equipped to perform any operation in urology. To that end, we train our young men in the proper technique of perineal, suprapubic, and transurethral prostatectomy. Each of these has its place in urological surgery. By limiting his surgery to one of these methods only, the operator limits his usefulness to his patients.

Widespread interest has been manifested in the past two decades, by both the medical profession and the laity, in transurethral resection of

the prostate In 1913, Hugh Young developed a method of transurethral surgery for certain types of enlargement of the subcervical group of tubules This operation, called the Young punch operation, did more efficiently and less dangerously what the Italian Bottini operation (performed through an external urethrotomy wound) was designed to do Young's operation was modified and improved, in 1920, by the late John Caulk, of St Louis, who added a cauterizing element In 1926, at The New York Academy of Medicine, Maximilian Stern presented a resection instrument made for him by the late Rheinold Wappler This instrument was too small to be entirely effective, but it was soon improved by Bumpus, Collings, McCarthy, Foley, Kirwin, and others

A tremendous wave of enthusiasm swept this country and extended abroad, and for a time claims were made to the effect that open surgery upon the prostate gland was doomed to oblivion As the fanaticism subsided, there also died down the extravagant claims that transurethral surgery was an office procedure, and that any prostate of any size could be removed without the preliminary preparation of the patient which had reduced the mortality of the open operation from nearly 50 per cent to about 6 per cent It soon became evident that this surgical maneuver was not as simple as it had at first seemed One great harm done by its too ardent protagonists was that their claims gave every doctor who could manipulate a cystoscope the idea that he could perform the transurethral operation Such, of course, was not the case, and the mortality of these amateur surgeons was tremendous

Transurethral resection has a permanent and highly important place in surgery of the vesical neck, and with the passage of time its scope and limitations are being better defined It is true that the method has a slightly geographic aspect, most of those who believe in transurethral prostatectomy to the exclusion of the open operation, it has been noted, live in the Midwest

Before deciding which operation to perform in a given case, one must determine the type of enlargement present In general, it is our practice to remove by means of *transurethral resection* all enlargements of the middle lobe and of the subcervical group of tubules, all fibrous bars, and certain obstructions due to malignancy of the prostate We prefer to use the Kirwin rotary resectoscope as a rule

If the enlargement of the gland is mainly intravesical, *suprapubic prostatectomy* is the method of choice The operation employed is the

so-called Fuller-Freyer technique. In this procedure, the capsule over the most prominently presenting part of the gland is incised, and from this point the enucleation is accomplished. Care is taken not to split the anterior commissure as by so doing one often tears into the plexus of Santorini on the anterior surface of the prostate, greatly increasing the bleeding.

In all other cases, *perineal prostatectomy* is done. This includes enlargements which encroach on the posterior urethra. Prostatectomy for the removal of a malignant gland, or for long-standing chronic inflammation, is also accomplished through the perineum. A recent modification of the usual perineal prostatectomy, by the author, has reduced postoperative incontinence of urine to a minimum. This consists in plicating the membranous urethra just external to the apex of the prostate by the insertion of a mattress suture of ribbon gut.

Recently, patients suffering from enlargement of the prostate, who have passed the period of sexual activity, have been operated upon by means of a *subtotal prostatectomy*, which is accomplished as follows. The prostate gland is exposed by the perineal route in the usual manner. The lateral surfaces of the gland are exposed, which is usually easily accomplished as there are seldom any adhesions from these aspects of the organ. The apex is then cut across and the entire gland and capsule excised except for a small strip of the anterior commissure. The seminal vesicles and ampullae of the vasa deferentia are cut across. The neck of the bladder is brought in contact with the membranous urethra by means of a mattress suture which not only approximates these structures and plicates the urethra, but stops all bleeding as well, thus doing away with the necessity of packing.

Our results with this modified perineal operation are so good that we perform it by choice unless the patient is still active sexually. In the latter case, it is unwise to do this procedure as the seminal vesicles and ampullae of the vasa deferentia are cut across, and ejaculation is impossible.

Preliminary preparation of the patient is of the greatest importance irrespective of the type of operation selected. This consists primarily of properly managed drainage, which is accomplished either by (1) a suprapubic cystostomy, with suction drainage, or (2) an indwelling urethral catheter.

Complications in prostatectomy by any of the three techniques men-

CHART II
OPERATIONS FOR BENIGN AND MALIGNANT HYPERTROPHY OF THE PROSTATE GLAND
Dec 10, 1920—Jun 1, 1941

	Age Groups							Hospitalization			Results			Mort Rate	Total Cases
	50	51	60	61	70	71	80	Short est	Long est	Aver age	Cured or imp	Un changed	Died		
PERINEAL PROSTATECTOMY Benign prostates Malignant prostates	21	197	309	128	17			1	148	24	617	55	81%	672	
	2	20	46	22	4			1	106	27	81	13	13.9%	94	
SUBTOTAL AND TOTAL PERINEAL PROSTATECTOMY Benign prostates Malignant prostates	2	18	16	8				2	60	25	12	2	4.5%	44	
	2	4	14	1				5	125	31	18	3	14.2%	21	
SUPRAPUBIC PROSTATECTOMY Benign prostates Malignant prostates	4	35	74	25	4			1	90	25	128	14	9.8%	142	
		1	1	3	1			1	17	20	4	2	33.3%	6	
TRANSURETHRAL RESECTION Benign prostates Malignant prostates	92	174	189	88	11			1	77	10	523	9	3.9%	554	
	6	11	20	17	1			1	165	17	48	1	10.9%	55	
YOUNG PUNCH OPERATION Benign prostates	18	18	16	3				1	58	7	52	3	5.4%	55	
KIRWIN SHRINKAGE OPERATION Benign prostates	3	2	3	2	1			2	38	12	7	1	0	11	
TOTALS	150	480	688	297	39						1520	14	120	7.2%	1654

SUMMARY		Total Cases	Died	Mort Rate
Benign	1478	96	6.49%	
Malignant	176	24	13.63%	
Total	1654	120	7.25%	

tioned are approximately the same. The mortality rate is lower in trans-urethral prostatectomy than in the suprapubic and perineal procedures because the large majority of these operations are done on much younger men.

Chart II shows the results of these various procedures, in both benign and malignant enlargements, in the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital.

SUMMARY

Attention is called to the effect of disease of the prostate gland in the young as well as the old.

Young men are liable to acute and chronic inflammation of the prostate, sometimes producing abscess, requiring surgery, but more often causing low back pain, urinary disturbances, and sexual disturbances. Non-surgical treatment is indicated in the latter, this consists of massage, urethral dilatation, urethrovesical irrigations, chemotherapy, hydrotherapy, diathermy, and other forms of physiotherapy. Tuberculosis of the prostate occurs fairly frequently in young men, and is usually part of a progressive urogenital tuberculosis. Treatment, as a rule, is non-surgical. Sarcoma of the prostate, a rare disease that is almost invariably fatal, affects young men and even children relatively often.

Appropriate diet and medication are indicated in all prostatic conditions.

Older men are subject to prostatic calculosis, and all forms of obstructive prostatism, both benign and malignant. Appropriate surgical methods must be applied after careful investigation has revealed the exact conditions that prevail.

In less than 5 per cent of cases of carcinoma of the prostate gland is the malignancy discovered in time to effect a cure by total extirpation. This is because there are no symptoms in early stages of the disease. It is therefore an important duty of the general practitioner and the family doctor to do a rectal examination on every male patient over 50 years of age, and to investigate thoroughly every case in which the prostate is not perfectly normal.

INFECTIONS OF THE MOUTH, PHARYNX AND UPPER RESPIRATORY TRACT*

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ACUTE PYOGENIC INFECTION OF THE TONGUE

HOWEVER important the tongue may be in its other relations to life and surgery, as the site of acute pyogenic infections it plays no great role. Only thirty cases of abscess of the tongue were reported in American and foreign literature in the 10 years between 1920 and 1930. In the last 10 years there have been only ten cases treated at the Presbyterian Hospital and Babies Hospital.

Various reasons are given for this immunity of the tongue. The covering epithelial layer is peculiarly thick and resistant. Surface infections do not enter easily. The blood supply of the tongue is very great, so that threatening bacteria are promptly attacked and destroyed. The structure of the tongue, almost solidly muscle, lacking connective tissue, gives pus no chance to spread. All these circumstances make tongue abscess rare.

Nevertheless, occasional cases do occur. Most of the cases start, not primarily from surface wounds of the tongue, but secondarily from acute infections of the tonsils. The usual history is that, several days after subsidence of an acute sore throat, pain begins in one side of the tongue. This increases gradually in severity, accompanied by swelling which may become so great as to interfere with breathing and swallowing. The usual constitutional symptoms of acute infections are present in varying degree. No one infecting organism is found exclusively. Streptococci are likely to predominate in the early abscesses, but later a mixture of many organisms will be found, with very foul pus being produced. As a rule the infection is limited to one side of the tongue, not penetrating the median raphe. When situated in the forward part, interference with breathing is caused by blocking of the

* Presented October 21, 1940 at the Graduate Fortnight of The New York Academy of Medicine

mouth and the crowding upward of the soft palate into the nasopharynx. If, however, the abscess is situated at the base, even though the swelling of the tongue may not be great, an accompanying edema of the larynx may threaten asphyxia.

The treatment in the early stages consists of hot irrigations and the use of antiseptic mouth washes. It must be remembered that there is great difficulty in swallowing in these cases, so it will be necessary to combat dehydration and starvation. Later, surgical interference will be called for. The abscesses well forward in the body of the tongue present no difficulty. A large incision and the placing of an adequate drain results in prompt relief. The abscesses at the base of the tongue are very difficult to reach for the placing of an incision. The swelling of the tongue makes both the use of a laryngeal mirror and a direct laryngeal speculum difficult. I have had experience with two lingual abscesses. One was situated in the body of the tongue, well forward on the right side. No difficulty was had in draining it. The other was at the base of the tongue, seemingly having started as an acute lingual tonsillitis. There was early edema of the larynx which called for scarification through the direct speculum. This abscess itself gave much more difficulty. The pain was great and swallowing was almost impossible. Only such a sloping surface could be exposed that an incision with a straight laryngeal knife through a direct speculum could not be made. It was thought at one time that an external submental incision, dissecting through the body of the tongue, would be necessary. Finally an incision was made with a right-angled laryngeal knife, guided by a mirror. This resulted in prompt relief.

SUBLINGUAL ABSCESES

These abscesses are for the most part secondary to bad teeth. Occasionally one will occur in connection with a calculus impacted in the sublingual duct, but this is rare. No one organism predominates but ultimately, as in all abscesses about the mouth, the pus will be foul. The course of development is that, pus having formed about the root of a tooth, the abscess ruptures through the bone into the floor of the mouth above the mylohyoid ridge, forming a swelling just under the mucous membrane. This situation is more likely to come about in connection with the incisors and canines than with the more posterior teeth. It must be remembered that the sublingual space communicates about the

posterior edge of the mylohyoid muscle with the submaxillary space so the pus may not be limited to the floor of the mouth, but may invade the neck as well. Another etiology must be mentioned. Since the introduction of local anesthesia by the injection of various solutions, a number of these abscesses develop following the extraction of teeth.

Whatever the course of development the symptoms are much the same. There is painful swelling under the tongue on one side which pushes that structure upward and backward, embarrassing breathing and swallowing. If the infection spreads beneath the jaw, a tender swelling develops in that region. The condition calls for adequate incision as soon as the pus can be localized. The drainage should be preferably into the mouth. If, however, submaxillary infection has developed, an external incision must be made parallel to the ramus of the jaw, displacing the submaxillary gland and thoroughly opening the submaxillary space.

It is necessary to describe here that inflammation of the floor of the mouth known as Ludwig's angina. This has such peculiar features that for many years it was described as a separate disease though there were always to be found eminent authorities who disputed that position, maintaining that it was only a form of submaxillary abscess.

Ludwig's¹ paper, published in 1836, gives an excellent description, not since surpassed. The infection arises as a rule in a decayed tooth or follows an extraction. The sickness begins with a slight fever, chills, fatigue, loss of appetite. A hard, painful swelling develops on one or both sides of the neck about the submaxillary gland, rarely about the sublingual or parotid. This hard swelling is the characteristic symptom. It progresses under the maxilla to the chin, perhaps to the opposite side, up over the jaw to the zygoma, down the neck to the clavicle, to the pharynx, to the larynx, to all the cellular and muscular tissue between the larynx and the mouth cavity. The tongue rests on a hard leathery mass which in the mouth feels like a hard ring along the borders of the maxilla. The patient can open the mouth only with distress and pain, speaking with difficulty partly from pressure on the larynx, and partly because the smaller throat muscles are affected. Swallowing becomes difficult on account of mechanical pressure.

For the first 4 or 5 days the general condition of the patient is fair. As the disease progresses, the skin over the swelling begins to redden, then some spots become soft, sink in, and give a feeling to the finger touching them as if there were air forming under the skin. Active

eruption of pus seems about to occur but this does not happen. At this stage, in the mouth cavity a part breaks through either in back toward the root of the tongue, or more often at the inner side of the maxilla, and an exceedingly foul, thin greyish or brownish red fluid is expelled. From then on there is rapid progress of the toxic symptoms, with death on the tenth or twelfth day in coma.

In some cases at autopsy the skin and immediately underlying cellular tissue were found unchanged. The deeper tissue was found to have disintegrated into a grey-black mass full of air bubbles. The salivary glands were unchanged. This suggests that the interstitial pressure is so great as to cause gangrene.

Ludwig's angina is summarized as follows

- 1 Comparatively slight inflammation of the throat itself
- 2 Peculiar "woody" hardness of the cellular tissue
- 3 Hard swelling under the tongue with swelling of the floor of the mouth on the inner border of the mandible, with red and sometimes bluish coloration
- 4 Progress of swelling with well-defined border of hard edema in the neck
- 5 Slight infection or absence of infection in regional lymph nodes while swelling continues in surrounding cellular tissue

This statement of Ludwig that the lymph nodes were not affected is of great interest since there has been some dispute as to this. Price,² reporting on five cases in an article published in the *Annals of Surgery* in 1908, stated that the infiltration travels by the lymphatic spaces and by contiguity. In a discussion of Price's paper, G. D. Davis disagreed with Price as to the transmission by lymphatics. He stated that, although there are lymphatics in profusion along the deep vessels of the neck, no large lymph nodes are found in this disease. Grodinsky³ in a very complete article published in *Surgery* in 1939 appears to demonstrate satisfactorily that the spreading is by fascial planes. This seems to be generally accepted by modern authors.

The treatment of Ludwig's angina has travelled the complete circuit from medical through surgical procedures and now seems about to become medical again. Ludwig reported one patient who was cured after 3 weeks by extensive blood letting, caustic applications to the swelling itself, very strong emetics, diet, and cataplasms. By 1885 surgi-

cal treatment was firmly established. A Barker⁴ published a paper in the *Lancet* in that year in which he reported two cases with recovery. He recommended early incision in the midline combined with free stimulation, the use of quinine and ferruginous tonics. Price, in his article already cited,² recommended very extensive incisions over the submaxillary triangles through the mylohyoid muscles, also in the midline between the hyoid bone and symphysis to the mucous membrane. If the sublingual tissues were very edematous, Price suggested that the mucous membrane be incised from the midline to the second molar tooth, then that a curette be inserted and the tissue curetted wherever there was a feeling of the tissue giving away. Four of his five patients recovered.

Rehn⁵ in 1922 expressed dissatisfaction with the generally recommended therapy of early and extensive incision from the outside. He lost three successive patients treated by that method. He recommended complete extirpation of the submaxillary gland.

Medical treatment was again hinted at in an article by Blassingame,⁶ in the *Memphis Medical Journal* in 1938. He suggested that sulfanilamide might influence the disease in the very early stages. Once necrosis had set in, however, he believed surgical drainage must be employed.

Hendricks⁷ expressed active dissatisfaction with surgical results. He reported one patient who died, although operated on within 24 hours of the onset of the disease. A second patient recovered on whom a tracheotomy was done at once and then drainage incision made. A third patient recovered on sulfanilamide alone. He thinks the possibilities of sulfanilamide therapy should be more vigorously investigated.

Leonardo⁸ reported twenty-one cases. This gave a rate of one case in 3630 hospital admissions. He insisted on very complete incision through the mylohyoid muscle, followed by the use of sulfanilamide postoperatively. This gave a mortality of 5 per cent. Thomas⁹ reported 40 per cent mortality in 106 cases.

However the use of sulfanilamide may ultimately influence this disease, undoubtedly the best present treatment is by early and very extensive incisions, the neck being explored until the abscess is found and freed. The results at the Presbyterian Hospital bear this out.

Experience at Presbyterian Hospital

In the past ten years there have been twenty-eight cases classified as Ludwig's angina at the Presbyterian Hospital. Reading the history

TABLE I
SUMMARY OF 28 CASES OF LUDWIG'S ANGINA

SEQUENTIA TO		TREATMENT	
Extraction of teeth	14	Pus released by incision	21
Sore throat	3	Incised, no pus found	3
Tongue abscess	1	Subsided without incision	4
Bad teeth	8		
Barber's itch	1	Total	28
Mastoidectomy	1	Died	2
Total	25		

and the examination of these cases one must conclude that there is a tendency at the present time to call all sublingual and submental inflammations Ludwig's angina. None of these cases strictly conform to the description originally given by Ludwig. They do not show the board-like hardness which he mentions and in most of them, when incised, a localized abscess was found. On the other hand perhaps we may conclude that the cases Ludwig described were in reality submaxillary abscesses which were not treated surgically and hence went on to a fatal termination. In any event, the treatment in this series has been much more successful than in many hitherto reported (Table I).

INFECTIONS OF THE LYMPHOID TISSUE OF THE TONGUE AND NASOPHARYNX

The lingual tonsils may be the site of quite as severe an infection as the faucial tonsils, though this is much more rare. In itself such an attack, even though caused by a streptococcus, is not as a rule serious. It must be remembered, however, that the infection is close to the larynx and may occasionally give rise to an embarrassing edema. It is probable, moreover, that some of the rare lingual abscesses begin as a lingual tonsillitis. It is necessary therefore to treat such infections with care. As a rule they improve quickly with local applications. Appropriate chemotherapy should of course be used.

INFECTIONS IN THE NASOPHARYNX

Occasionally a streptococcal infection will lodge in the nasopharynx. These patients will be very sick, not only on account of the distressing

local symptoms but because the toxemia is severe. There is, moreover, always the threat of an otitis media and its sequelae. Examination with a postnasal mirror will show the whole posterior wall of the nasopharynx to be plastered with membrane. Local treatment is difficult and the condition has been found to be very persistent. The use of chemotherapy may greatly alter this picture.

INFECTIONS OF THE TONSILS AND THEIR SEQUELAE

I shall limit my discussion to acute infections of the tonsils and their more important sequelae. Any discussion of diphtheria will also be omitted.

The tonsils are distributing points of infection. Secondary to tonsillitis any part of the respiratory tract, or the ears may be invaded. It has already been pointed out that an abscess of the tongue may be related to a tonsillar infection. The tonsils being distributors of infection, any means of limiting infection to them alone should certainly be used. Chemotherapy is one of these means. Our experience at the Presbyterian Hospital has been this, that sulfanilamide for instance, does not make much change in the ordinary course of a tonsillitis but that the complications are fewer when it is used. Once a complication has ensued, such as a peritonsillar abscess, surgical treatment will be indicated. Even then the drug should be continued after operation. The experience of Rhoads and Afremov¹⁰ at the Cook County Hospital and Evanston Hospital has been less favorable. Treating thirty-one patients with sulfanilamide, thirty-six patients untreated being controls, appeared to make little difference in the results. In fact they concluded that the drug had no favorable effect on the severity of the symptoms, the period of incapacity or the incidence of complications. Moreover, in some instances, the reactions were serious enough to cause concern. They question the routine use of sulfanilamide in uncomplicated cases of tonsillitis and pharyngitis. They do, however, urge the use of the drug when complications occur, such as cervical adenitis, paranasal sinusitis, or otitis media.

At the Presbyterian Hospital our results have been checked in connection with otitis media. In a group of 100 children, half received sulfanilamide, half did not. In those receiving the drug, the duration of the discharge was on the average, 8 days. In those who did not receive the drug, the average duration was 12 days. Two per cent of the treated

cases had mastoidectomies, whereas 12 per cent of the untreated cases had mastoidectomies

Of the various sequelae, I shall discuss laryngeal abscess, laryngo-tracheobronchitis, and peritonsillar abscess

LARYNGEAL ABSCESS

A number of laryngeal abscesses are caused by the trauma of a swallowed foreign body. In such cases the train of events is easily followed. After the pain of the injury, there succeeds a period of more or less comfort. Then, as infection ensues, pain on swallowing develops, and perhaps some dyspnea. It is the characteristic of these traumatic abscesses, however, to be limited in their effect. Many of them are confined to the epiglottis. Examination with the mirror reveals a limited swelling which may already show a whitened area where the pus is pointing. Should threatening edema develop, the larynx should be exposed with a direct speculum, or a mirror and the edematous area scarified. As soon as an area of pointing presents itself, the abscess should be incised. As a rule healing is prompt.

The laryngeal abscess secondary to acute streptococcal pharyngitis or tonsillitis is much more stormy in its course. The infecting organism is as a rule an extremely virulent streptococcus. Pain in the throat is from the beginning severe, and difficulty in breathing may soon follow. Examination of such a larynx shows great swelling of the epiglottis and the aryepiglottic folds. At so early a stage no focus can be seen. It is customary to use for these cases, steam inhalations, sprays of cocaine and adrenalin and the like. These measures may at times suffice. The safest procedure however, is early and deep incisions made in the epiglottis and the folds. These incisions will relieve the edema. An abscess will probably form later and may discharge through these incisions or may need separate incisions. Occasionally the infection will penetrate to the perichondrium lining the inner surface of the thyroid cartilage. An abscess will then form in the pyriform fossa which must be drained by external incision in the neck. Such an abscess, undrained, may penetrate to the vascular sheath and invade the mediastinum.

The treatment, then, of acute laryngeal abscess is early scarification. A tracheotomy will thus be avoided. Later, drainage of localized pus must be effected by incision under direct exposure. If the pus reaches the pyriform fossa, an opening through a window in the thyroid cartilage

TABLE II

ANALYSIS OF FIVE CASES OF ABSCESS OF THE LARYNX

1 Sore throat for 24 hours, epiglottis swollen, ruptured on one side, opened the other	4 Sixteen days old, ailing, abscess found at autopsy
2 Pain for 36 hours, swelling left side of larynx, ruptured	5 Pain in throat 2 weeks, admitted choking, tracheotomy, incision of laryngeal abscess, ligation of internal jugular vein, drainage of lung abscess, died
3 Foreign body day before, larynx blocked, tracheotomy, discharged in 7 days	

and external incision low down in the neck may be required (Table II)

It will be seen that two of these cases came from infection and one from a foreign body. Only one of them had to be opened. Two ruptured spontaneously, one case of foreign body required a tracheotomy within 24 hours. In a paper published by Henry P. Schugt and myself,¹¹ five additional cases were reported. In addition I have seen three others. There have been two deaths among the thirteen patients, one due to mediastinitis, the other to lung abscess.

LARYNGOTRACHEOBRONCHITIS

In my experience this begins with terrifying suddenness. A child may complain of sore throat at noon and by evening be at the point of death from strangulation. Examination of the pharynx may show only a red throat. Examination of the larynx with the direct speculum shows the tissue fiery red, perhaps covered with white membrane. The cultures do not give uniform results, various forms of streptococci or pneumococci show. Two of the most severe cases I have seen showed the influenza bacillus in the throat culture and also in the blood stream. One of these patients recovered when given sulfanilamide.

My procedure is to do a tracheotomy if there is any difficulty in breathing. I have tried combating the dyspnea with steam and oxygen-helium in a tent. The latter beyond doubt relieves dyspnea for a time, but cannot maintain the improvement. My procedure is to pass a bronchoscope through the inflamed larynx, and perform a tracheotomy on that as a guide. Observation at that time shows the bronchial mucous membrane already inflamed, perhaps covered with membrane. The pa-

TABLE III

SUMMARY OF THE 18 CASES OF LARYNGOTRACHEOBRONCHITIS

Recovered	12	Deaths in tracheotomies	6
Died	6	Patients given sulfanilamide	12
Tracheotomies	10	Deaths in sulfanilamide group	3

tient is then kept in steam, sodium bicarbonate solution is instilled through the tracheotomy and perhaps bronchoscopy repeated many times for the removal of the membrane. The mortality of this disease has been 50 per cent. There was a remarkable increase in laryngo-tracheobronchitis in the years 1938 and 1939. George Brighton working with the patients at Babies Hospital, including also private cases, found the mortality among the tracheotomized cases to be 40 per cent. He makes the interesting suggestion that this may be a virus disease, not due to any bacterial organism, which would explain the cultures being so varied. He bases this idea on experimental work which has been done in connection with laryngotrachitis in chickens. This disease in these animals has proved to be due to filterable virus. The pathological changes found in the mucous membrane of the trachea are similar to those found in human beings who have died of this disease. Although it is not always safe to compare results in animals and human beings, the close resemblance of the two diseases is at least suggestive. Brighton's report is based on twenty-eight patients all of whom had tracheotomies. Many of these were private patients who perhaps received more intensive nursing care.

It will be seen from Table III that six out of ten of the patients who required tracheotomy died. Sulfanilamide appeared to make very little difference in these extremely ill children. One patient died 6½ hours after admission although he was given prontosil intravenously.

PERITONSILLAR ABSCESS

W. Krainz¹² explains the tendency to peritonsillar abscess in those subject to chronic tonsillitis in the following way. The crypts of the tonsils are always more or less occupied by a mass consisting of cell detritus, food, bacteria and the like. Owing to the action of the palatal muscles during swallowing, the crypts are for the most part kept clear

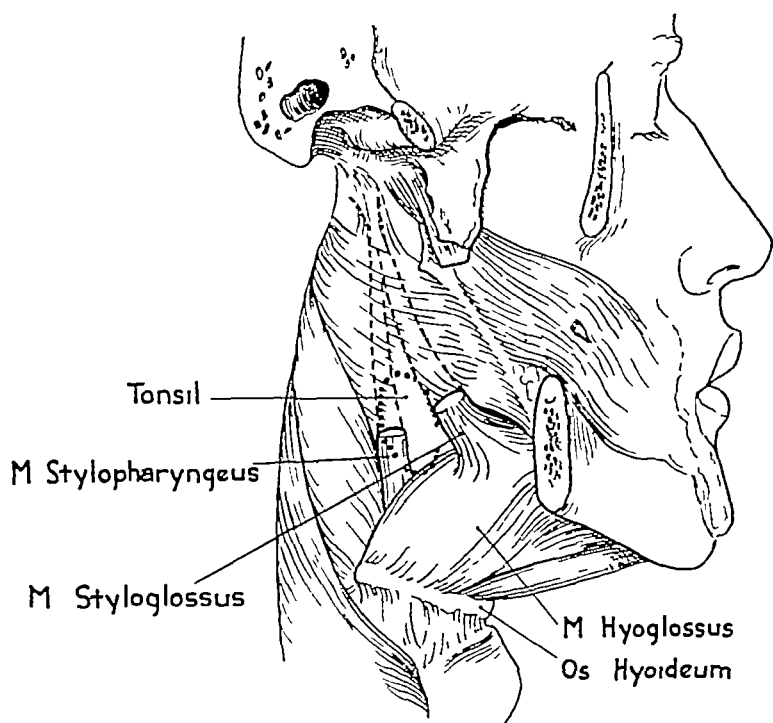


Fig 1—The anatomy of the tonsillar region

of these masses. When there have been many attacks of tonsillitis, however, there is a deposit of fibrous tissue in the tonsil which prevents the emptying of the crypts. Then the masses in the crypts become infected and abscesses are formed.

Such abscesses begin in the depth of a crypt. Swelling about the mouth of the crypt blocks off the drainage and the abscess ruptures outward into the space between the tonsil and the walls of its fossa formed by the pillars in front and behind and the superior constrictor of the pharynx to the outer side. As a rule the abscess develops high in this space and points forward between the anterior pillar and the tonsil at its upper pole where it can be opened after 5 or 6 days. The result then is immediate relief.

Sometimes the result is not so happy. The abscess may be low between the tonsil and the posterior pillar. Then it can be reached for incision only with great difficulty. The result may finally be spontaneous rupture without the intervention of the surgeon. Both of these results, though the patient has suffered much for a number of days, are considered satisfactory.

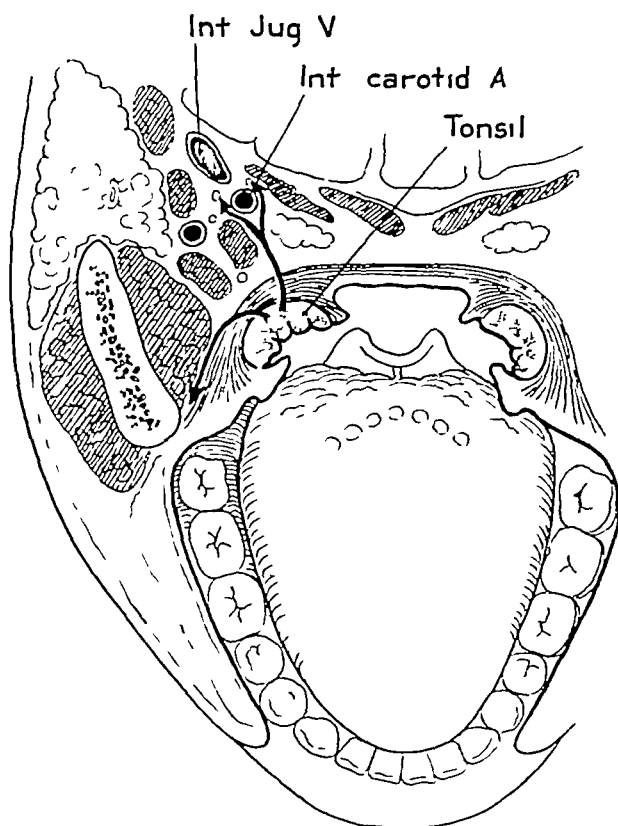


Fig 2—The relation of the tonsil to the great vessels

Things, however, may not turn out so well. The surgeon may make several incisions without finding the abscess. The tonsil may continue to protrude into the throat, pain and dysphagia may continue and a swelling appear outside in the neck. To explain this we must consider the anatomy of this region. It has been said that the tonsil lies on the superior constrictor of the pharynx. This muscle forms the inner wall of the pharyngomaxillary space, bounded on the outer side by the maxilla and internal pterygoid muscle, above by the base of the skull, behind by the muscle of the vertebral column. It is divided into an anterior and posterior compartment by the styloid process and its muscles. The anterior compartment contains the parotid gland and communicates below with the submaxillary space. The posterior compartment contains the great vessels of the neck in their sheath which runs into the mediastinum.

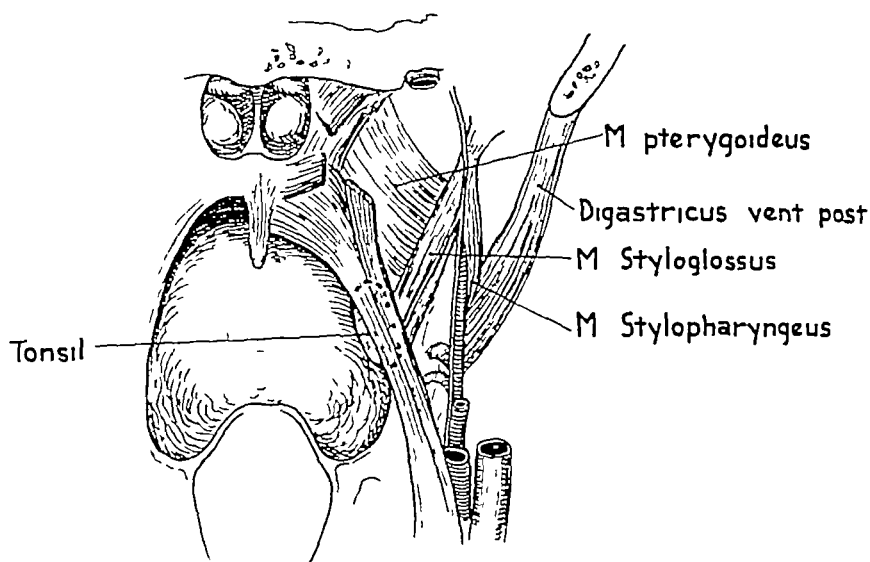


Fig 3—The relation of the tonsil to pharyngeal muscles

The peritonsillar abscess which does not respond to incision and drainage has broken through into the pharyngomaxillary space. This accident of course greatly increases the danger to the patient, the degree depending on where the rupture takes place. The pus may take one of four directions. If it ruptures high into the anterior compartment, it will lie between the internal pterygoid muscle and the pharynx. There will be no external swelling but considerable trismus. If the rupture occurs lower down, the pus will follow the styloglossus muscle to the floor of the mouth and form a submaxillary abscess. It will not pass down the neck. If the pus passes behind the styloid process it may reach the posterior triangle of the neck at the base of the skull. This very rarely happens. In one of the few cases reported there was severe hemorrhage because in the passage of the pus beneath the great vessels, the internal jugular vein was eroded.

Pus pointing into the posterior compartment is much more likely to break into the sheath of the great vessels and pass down the neck toward the mediastinum. Even though this does not occur, the mere contact of the pus with the vein may cause thrombosis of the internal jugular vein with consequent general sepsis. It should be recalled moreover, that the tonsil lies in a plexus of veins. Thrombosis of these small radicals may extend to the internal jugular.

Pus may reach the vascular sheath in still another way secondary

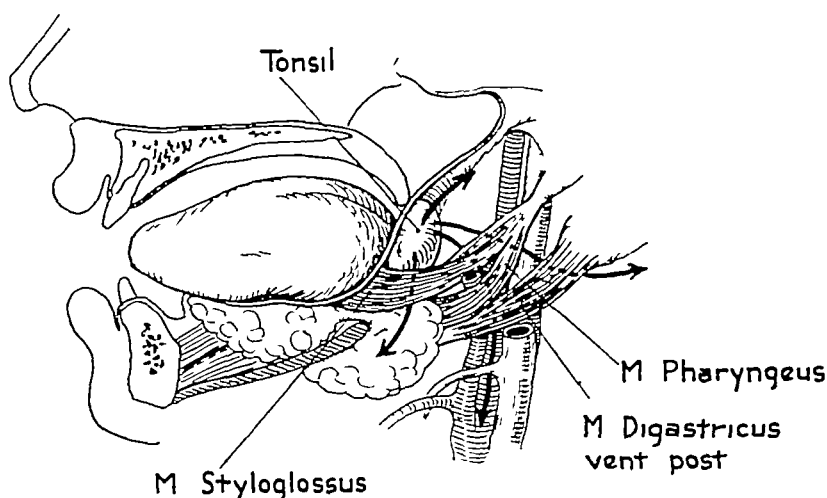


Fig 4—Four possible paths along which peritonsillar abscess may travel when it has broken into the pharyngomaxillary space

to tonsillar or peritonsillar abscess, namely, through the lymphatics. If the glands along the great vessels break down and suppurate, the pus will be in contact with the vein.

A number of so-called peritonsillar abscesses occur secondary to the extraction of teeth, and the formation of a submaxillary abscess. In these cases the pus has followed backward the route which leads from the pharyngomaxillary along the styloglossus muscle to the submaxillary space. These are not in reality peritonsillar abscesses. They are from the start deep abscesses of the neck.

Upon the entry of the pus into the neck, new symptoms are added to those of peritonsillar abscess. Severe trismus develops in connection with abscesses of the pharyngomaxillary space. The submaxillary abscesses develop characteristic local symptoms. The abscesses along the vascular sheath are liable to cause edema of the larynx and difficulty in breathing of such a degree that a tracheotomy may have to be considered. The chills and fever of septicemia will follow infection of the vein.

TREATMENT OF PERITONSILLAR ABSCESS

In view of the dangerous complications which may arise in connection with peritonsillar abscess many have been discontent with the ordinary treatment, namely, hot irrigations till the pus points, then,

incision into the anterior pillar. The suggestions have been (1) separation of the superior pole of the tonsil, (2) partial tonsillectomy, the superior pole of the tonsil being removed, (3) total tonsillectomy. These operations are done during the acute attack.

There appears to be little more to be said for separation of the superior pole of the tonsil than for simple incision or for separation of the anterior pillar from the tonsil with a tonsil hook, a procedure which has long been carried out at the Presbyterian Hospital. When this procedure is successful, it suffices but the pillar may adhere again and so block drainage and, moreover, low posterior abscesses are not reached.

Schroeder¹³ reports on the treatment of peritonsillar abscess at the Sundby Hospital, Copenhagen, 92 patients were treated by the usual peritonsillar incision and made a satisfactory recovery. Fifty-six patients needed further operative treatment for the following reasons. In fifteen cases no pus appeared after repeated incisions and the temperature remained high, in thirteen cases the abscess was followed by nephritis, in eleven cases edema of the glottis occurred, in seventeen cases parapharyngeal abscess formed, in two cases there was thrombophlebitis of the internal jugular vein, in forty-three of these patients detachment of the upper pole was done, in five cases on both sides, in the remaining thirteen patients, total tonsillectomy was done. All of these patients recovered without further complications. The procedure was carried out under local anesthesia.

As early as 1911 (Winckler¹⁴), total tonsillectomy during the attack was suggested and carried out. Salingre¹⁵ (Helsingfors) is one of those who advocates this procedure, especially in cases threatened with complications, or in cases in which the abscess is low down or far back. He uses local anesthesia, injected into the palatine foramen and into the lower pole of the tonsil. He employed this procedure in fifty-four cases, all were successful.

Other authors are even more enthusiastic than Salingre, unreservedly recommending tonsillectomy during the attack and even advocating the removal of the tonsil on the opposite side. Blashki¹⁶ is one of these. He reports thirteen patients operated on under general anesthesia. One of these died from heart failure, the anesthetic risk being known beforehand. W. Klose¹⁷ urges double tonsillectomy on these patients because of the frequency of concealed abscesses. In twenty-four of his patients an unsuspected abscess was found on the opposite side on the occasion

of abscess tonsillectomy. In eleven patients abscesses developed after repeated incisions had supposedly healed the peritonsillar abscesses. In eight patients entirely unsuspected abscesses were found on tonsillectomy. He maintains that many more concealed abscesses will be found if sought for.

One of the advantages especially emphasized by those who advocate tonsillectomy during the attack of peritonsillar abscess is that this procedure makes possible the drainage of pus which has already penetrated to the parapharyngeal space. The tonsil being removed, the fistula leading to the extrapharyngeal collection will be exposed. The enlargement of this fistula will promote drainage into the pharynx and thus external operation will be avoided.

To those who fear the spreading of the infection by tonsillectomy in the presence of an abscess, the article by Gangl-Battig¹⁸ may be pointed out. This author has demonstrated that the height of the attack is the very time when the resistance of the patient is highest. Once a well demarcated abscess is formed, the greatest danger is over. Drainage then becomes the greatest necessity, and this is best accomplished by tonsillectomy. Surely no one hesitates to remove an appendix in the presence of pus. Why not, then, tonsillectomy?

It may be taken for granted, then, that a good case may be made out for tonsillectomy during the active stage of peritonsillar abscess, especially in cases threatened with complications. I am not quite prepared, however, to recommend the procedure unreservedly. Some bad results have been experienced, especially when the opposite sound tonsil has also been removed. At the Presbyterian Hospital only a meager number of cases can be reported on. These were all done under general anesthesia, only the diseased tonsil being removed. The results were most gratifying. All pain appeared to cease at once, and all patients were able to eat freely within 24 hours.

Little has been said as to the use of sulfanilamide in these cases. This is because our results have not yet been sufficiently numerous to make them of value. A number of cases have, to be sure, resolved without developing pus, but you will note on the table that this has also been brought about by hot irrigations. Reports in the literature on the use of sulfanilamide are as yet few. Hubert and Leroux¹⁹ reported on twenty-two patients treated with this drug. Sixteen of these recovered without surgical intervention, and in six, surgical intervention was nec-

TABLE IV
FEATURES OF 320 CASES OF PERITONSILLAR ABSCESS

Previous attacks	49	Complications	37
Previous tonsillectomies	9	Hemorrhage	6
Tonsillectomies	40	Otitis media	15
Ruptured after irrigations	57	Cellulitis of neck	8
Incised	162	Acute cervical adenitis	6
Incised more than once	19	Arthritis	2
Arose from teeth	39	Rheumatism	4
Resolved on irrigation without pus	19	Erysipelas	5
Incised after prontosil	7	Abscess of pharynx	11
Resolved after prontosil	25		

essary They conclude that if given early sulfanilamide may prevent suppuration, but that every formed abscess must be opened Sonnen-schein²⁰ made a report on two patients In one of these, the abscess re-ruptured spontaneously, in the other, it resolved without suppuration These reports are too few to justify any conclusions

In the past 10 years we have had 320 cases of peritonsillar abscess which I show in tabulated form (Table IV)

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THE DOCTOR IN COURT*

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THIS meeting, having as its subject "The Doctor in Court," concludes the series dealing with medical aspects of personal injury actions and disability insurance. The symposium was arranged with the cooperation of The New York Academy of Medicine and the Medical Society of the County of New York. We are especially indebted to Dr. Malcolm Goodridge, President of The New York Academy of Medicine, and to Dr. Walter P. Anderton, now past President of the Medical Society of the County of New York, for their advice and their assistance.

At the last three meetings we listened to interesting and instructive lectures on certain medical aspects of trauma and disease. The large attendance showed the keen interest of the Bar. Apart from their intrinsic value, these lectures will, I am sure, serve to bring the two great professions of medicine and of law closer together, they will foster a deeper knowledge of the relations of those professions to each other. They will, we hope, serve as the keystone of a new and a better understanding and be the beginning of a regular periodical interchange of lectures and discussions that will help to solve our mutual problems.

If I may be pardoned a personal reference, these meetings have for me a special significance. As a youth, I wanted to be a doctor. Every penny I could save went to the purchase of old medical books and magazines found on the second-hand book stalls of Fourth Avenue. I certainly acquired a motley collection. Every hour I could spare from college work was spent in visiting dissecting rooms and the operating theatres. But my youthful hopes were not to be realized. I did not enter medical school, but I never lost my early love for the science and the art of medicine.

By one of those compensating dispensations, from an early date in my work as a lawyer, I found myself professionally engulfed in a medi-

* Presented February 25, 1941 in the symposium conducted by the Association of the Bar of the City of New York in connection with The New York Academy of Medicine and the Medical Society of the County of New York. Judge Shientag was Chairman of the Committee on Post Admission Legal Education of the Bar Association, under whose auspices these lectures were given.

cal atmosphere With the Factory Commission came the problems of industrial hygiene and occupational diseases With the Labor Department and the Bureau of Workmen's Compensation came the problems of medical examinations and treatment and the fascinating and absorbing study of the relationship between trauma and disease On the Bench came the most frequent contact with problems of accidents and disease, of mental sickness and incapacity So, while I have been lawfully wedded to the law, medicine is still my mistress, one that will always be wooed with longing and with ardor

Indifference is always a grave peril, for rust will crumble a metal where blows may only tend to harden it If doctors complain of their treatment in our courts of law, and lawyers find fault with the way doctors testify, we should not remain indifferent The sensible thing is to ascertain the facts, to find out what is causing the discord, to decide upon the proper remedies, and to see that they are carried out

The doctor plays a large and a vital part in the administration of justice Yet what does the average doctor know about procedure in the courts, and what does the average lawyer know about the practice of medicine and the problems of his medical brethren?

For the medical profession we, of the law, have the greatest respect and admiration We thrill to the reading of the ancient Hippocratic oath, that lofty and most unselfish dedication to the service of humanity, to the alleviation of misery, suffering and distress The mission of the doctor is of the highest and noblest kind, in assuaging pain, in restoring health, and in turning back the hand of death

We rejoice that the glorious march of science in medicine has always inured to the benefit of mankind, and we pray God that it may ever continue to do so

Our two great and honorable professions have the same high ideals of truth and of loyalty, the same continuity of tradition, the same impulse to shake off the shackles of outworn dogma and of obsolete rules which hamper progress We in the law have much to learn from you doctors in connection with your educational methods, your clinical instruction in small groups, the even balance you maintain between the study of the science of medicine and the practice of its art

We have much to learn from you in connection with your emphasis on the prevention of disease, we have much to learn from you about your systematic postgraduate instruction, the splendid educational ac-

tivities carried on by your medical societies, your encouragement of the study of the history of medicine and the literature of your great profession—studies which broaden the outlook and liberalize a man's conception of his calling. We lawyers derive inspiration from the works of the great masters of medicine, the writings of Osler and Cushing in this country and of Allbutt and Moynihan in England.

So you see, my medical brethren, that when you enter the home of the law you are among friends. But, you say, that's all very well. We like to meet lawyers socially, but in the court room—that's a different story. But is it a different story, and what makes it so? What is there to do about it?

The experienced and distinguished speakers of the evening will elaborate on this theme. They will discuss the duties and responsibilities of the judge, the lawyer and the doctor when medical testimony is given in court. Let me commend to my brethren at the Bar the injunction of Ecclesiasticus: "Honor the physician with the honor due unto him." A doctor appearing in court is entitled to the respect, the courtesy and the consideration due to a professional brother. Unhappy is the lot of a client whose lawyer is foolish enough to resort to a rude, unfair cross-examination of a doctor. Indeed it is the rare exception for a Judge to sit by and ignore the extravagances of bitter and misleading cross-questioning.

The subject of the medical expert and of the much abused hypothetical question will be discussed from different angles by the speakers of the evening.

It has been my observation that of doctors who give testimony in court there may be said to be five kinds:

- 1 The careless doctor—careless in his appearance, in the way he has kept his records, in his manner of testifying, careless in answering before he has even grasped the purport of the question.

- 2 The doctor who doubts everything—the morbid doubter, he has been called. He is generally a man who knows his subject, but is constitutionally unable to make up his mind and to express any opinion. His testimony does nothing to aid the cause of his patient or the administration of justice.

- 3 The noisy, pompous doctor—of boundless and confident conceit. He knows and gives the answers before he is even asked, with an evident and irritating sense of superiority he talks down to the judge and jury,

and is so cocksure of everything that he soon becomes the architect of his own ruin. He should bear in mind the observation of a distinguished artist, that the man who paints with a big brush is not of necessity a great painter.

4 The technical, lecturing doctor—who seeks to impress the court and jury, generally without success, and attempts to substitute for ability and for a candid and sound medical opinion what has been aptly termed “the mutterings of robustious nonsense.”

5 The sensible, competent doctor. Fortunately, most of those who testify in court belong to this class. This doctor carries himself with unassuming professional dignity. He is prepared for accuracy in his testimony. He answers questions directly, without long and learned dissertations. He uses a minimum of technical terms, and when he finds it necessary to use them, explains them in plain, simple language. He does not allow himself to become the victim of a not uncommon human capacity—the capacity for self-deception. Nor, to use the language of Dr. Da Costa, is he the type of expert witness who possesses “one of those trained memories which is able to remember everything advantageous and nothing harmful to his side of the case.” He is as sound as he is fair, and impresses you with the force of his conviction and his fine impartiality. He is the master of his temper and slow to anger, no matter how great the provocation. His patients call him blessed, and to the court he is “As an hiding place from the wind, as rivers of water in a dry place, as the shadow of a great rock in a weary land.”

Parenthetically, I might add that there would be no difficulty in classifying lawyers along somewhat the same lines.

Whether, to what extent and under what circumstances, the presiding judge has or should be given the power to appoint an impartial medical expert will be considered later in the evening. Let me say at this time that for the most part we must rely on education to improve the position of the doctor in court. The more the lawyer knows about the medical aspects of his cases the less opportunity there will be for prejudiced, incompetent or misleading medical testimony, the more the doctor knows about the court procedure and the elementary rules of evidence the less the likelihood that he will leave the stand feeling that he has been placed in a false light or that he has been improperly taken advantage of by his legal inquisitor. It is this process of education, not casual or haphazard, but continuing at regular intervals, that it is hoped

meetings like this will stimulate

The Bar is eager to cooperate with the medical profession to eliminate abuses and just causes of complaint. From what I know of the doctors, they will meet us more than half way in this most worthy endeavor. By working together in a spirit of mutual respect, tolerance and helpfulness, we shall most surely and confidently advance along the road of progress.

THE DOCTOR IN COURT*

GEORGE Z. MEDALIE

Vice President, The Association of The Bar of the City of New York

THE votaries of law and of medicine meet tonight in an endeavor, by frank discussion, to find a way in which both can cooperate to serve the cause of justice. The problems involved are not peculiar to the field of medico-legal jurisprudence. Other phases of the law present similar problems. The Bar Association, where we meet this evening, maintains a host of committees dealing everlastingly with similar problems. On occasion, these committees believe that they have found solutions. These are subjected to discussion and criticism but do not always meet with legislative or judicial approval, or, for that matter, with the approval of the Bar itself. And even when a solution for a particular defect in the administration of law and justice is agreed upon, new creaks are found in the machine, and effort at readjustment is renewed.

Justice is a human and practical institution. Only a constant and zealous regard for its efficient working on the part of those who participate in it, or are affected by it, can maintain it as a living and useful reality. On that aspect of justice in which the physician and the lawyer are jointly interested, it is refreshing to know that there is the desire for mutual cooperation and that the courts, in whom vests the greatest responsibility, join in our efforts for better understanding and mutual aid.

I think, perhaps, that I am in error when I say that both professions display this interest. It would be an error indeed if I left the impression that the Bar as a whole, and that Medicine, as a whole, felt a keen interest in the problems which we consider, for the fact is that most members of our two professions have no contact with medico-legal problems, and therefore have only a passing interest in their solution.

However, this need not be a cause for deep regret, for usually responsibility and interest attach only to those who meet with particular problems in the course of their daily work.

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In subject matter and in operation the work of the physician and of the lawyer seems set apart by almost astronomical distances. But there is one respect, at least, in which both professions are quite alike. If my medical friends will not take umbrage at this remark, I should like to observe that both lawyer and doctor learn what they know as a result of trial and error.

The law is not static and neither is medicine. What was sound doctrine for judge and lawyer a generation ago is unlearned by the elders of the profession, and never taught to its neophytes. What was good policy in the administration of justice a century ago sounds fantastic in this new and constantly changing world.

I need hardly add the obvious so far as medicine is concerned. Its field of knowledge is wider today, its factual data greater than a generation ago, there are new techniques, new opinions as to the nature, cause and character of disease, new methods of treatment, and in many ways there exists an entirely changed outlook.

It is because of this similarity in both fields, namely, our learning by trial and error, our constant change of opinion and viewpoint, and the acquisition and discarding of beliefs, that the doctor and the lawyer can and should understand each other and in dealing with matters of common interest and mutual contact find ways and means, not simply to get along, but to discuss those questions in which the public interest is concerned in the administration of justice.

Shortly after Judge Shientag gave me this assignment, I tried to find out how doctors and lawyers felt toward each other as a result of their contacts in the court room. I made no attempt to emulate Dr. Gallup, but in my own crude, unscientific way, I convinced myself, as a result of a considerable number of interviews, that the doctors as a whole were not satisfied with the lawyers, and that, generally speaking, lawyers were sometimes dissatisfied with their medical friends.

And, I may add, that the doctors, too, have expressed considerable dissatisfaction with the courts and the law.

Insofar as laymen have given any thought to the conduct of medico-legal cases, there is no lack of dissatisfaction among them as to all of us—judge, lawyer and doctor, and the law as well, but, after all, we are only human beings and, conscientious though we may be, we are far from perfect. But we may console ourselves at least with one thought. We come together to consider our subject in the public interest. So that

justice may be done, as nearly as that is humanly possible, we are anxious that neither side permit error to continue, that no one frustrate the search for the truth, or make the task of any concerned in the process difficult or unpleasant

In recent years, some have come to question whether the judicial process is the most effective method for deciding the medical problems that arise in connection with the numberless issues in which the physician may give testimony. At present, our courts are concerned with medical testimony mainly in negligence cases. These deal in large measure with injuries arising out of automobile accidents.

Injuries attributed to the operations of common carriers play a smaller part. There are also a very considerable number of cases on the calendars of our courts which concern themselves with personal injuries arising from the operation of property. Then, too, there are the malpractice cases.

In the past, and before the Workmen's Compensation Law became operative, factory accidents furnished a considerable contribution to our tort calendars. Not infrequently in probate proceedings, questions arise as to the testamentary capacity of the testator, but for the total number of wills offered for probate, such contested issues that actually go to trial are really few in number. Occasionally, too, arises the issue of the mental incompetency of a person whose means are substantial enough to give his family serious concern. But these issues, too, are tried only now and then.

In criminal cases, there is also supposedly a wide field of litigation involving the sanity of the accused. Actually, however, such issues are tried only occasionally. But most discussion of medical expert testimony on the part of the public and in our public prints arises from that particular group of cases.

It is less important that a lawyer earn a fee for the trial of a case, and that the doctor receive compensation for giving expert testimony in a court, than that the truth be determined speedily with as little complication as possible, and as inexpensively as the situation will permit.

Thus, from time to time, various proposals have been seriously brought forward, designed to do away with supposedly biased testimony on the part of the physician, to eliminate conflicts in expert opinion, and to assure speedy and inexpensive justice to claimant and defendant in civil cases, and to the public and the defendant in criminal cases.

I do not mention these proposals because I either favor or oppose any of them I call attention to them only because these changes in our administration of the law come to us because there is dissatisfaction in this aspect of our judicial system

Serious minded people have been impressed with conditions which, rightly or wrongly, they consider hamper us in the search for truth and in the determination of rights They point to the fairly satisfactory operation of our Workmen's Compensation Laws as a substitute for needlessly contested trials in our courts in which, they say, evidence, including medical testimony, is so presented that it becomes a question of gamble and skill rather than of justice and of truth in the making of judgments

Few go so far as to suggest that all personal injury cases be determined by any such procedure and the elimination of our courts, but there is a not inconsiderable group who would start now on the basis of the adoption of a compulsory automobile insurance law to put that large group of personal injury cases into the field of administration, and practically out of the reach of our courts

Many suggestions for the determination of issues of insanity and criminal responsibility for similar reasons have been made, so that there would be two trials, one, the issue of guilt, and the other, the issue of sanity

It has also been proposed that there be impartial experts, not selected by either side, in both civil and criminal cases I do not now offer any opinion as to the merits of these proposals They can be separately considered, but I refer to them now because their origin is to be found in the intense dissatisfaction or, if you will, misunderstanding as to the character of medical testimony given day by day in our busy courts

I think we might well admit, both as doctors and as lawyers that, rightly or wrongly, that portion of our work that deals with medical testimony is not approved by the public In fact, I suspect that it never was We have only this solace—that rarely in any era did the public ever approve of the courts one hundred per cent Whatever confidence Americans have in their judicial tribunals, yet, to the extent that they yield to the human impulse to find fault with their elders and betters, they have at least indicated some disapproval in connection with the work for which we, as lawyers and doctors, are jointly responsible

Let me make one more reflection on our joint labors It is true that

criminal cases, involving issues of insanity in which there are actual trials, are few and far between, but these are the most spectacular of all litigated cases. These trials attract the elite of the Fourth Estate and for these cases there is preemption, except in the event of war or of earthquake, a first call on all space up to the actual exclusion of department store advertising. A mere handful of these cases causes the public to sniff at both of us. Few of us in either profession have been concerned with these things, but the net result has not been for our good nor have we left the public and the gentlemen of the press with anything but a distorted picture of our joint efforts.

The Thaw case, a few may be old enough to remember, left a lasting bad taste on the battle of experts. In more recent years, an inquiry as to sentence on pleas of guilty in a murder case, the Leopold and Loeb case, attracted nation-wide attention, and the experts were held up to derisive discussion because, supposedly, of a difference of opinion on their part, but actually, I think, because of differences of opinion on the part of the public as to what disposition the court should have made in pronouncing judgment.

While there is a basis for public dissatisfaction because of cases of this character, it must be remembered that the incentive to public interest comes primarily from a morbid interest on its part, partly a love for lurid detail, and partly an expression of a mob's sadistic desire to wreak vengeance upon the unpopular perpetrator of a revolting or unapproved murder.

There was a time when an expert, particularly a physician or surgeon, had a status, and a very respectable one, in the courts. One may go back to the 14th Century, when a judge who wanted medical advice would call a physician for whom he had a high regard and whose advice and opinion he accepted on a fundamental issue of the case.

But, over a century and a half ago we reached the point where it was possible for a judge to tell the House of Lords "Hardly any weight is to be given to the evidence of what are called scientific witnesses."

That tune continued to be played for a few generations, but I think it may safely be said now that, on the whole, medical and other expert scientific testimony is given a fair chance in our courts with a minimum of judicial derision and is even occasionally relied on in our appellate courts in finding a basis for sustaining or reversing a judgment.

I realize that, when a wealthy family finds that one of its members is

charged with murder, or some other criminal offense, there is the temptation to hire experts in a desperate attempt to ward off what would otherwise be the inevitable

Doubtless, too, that situation presents itself to the less fortunate And, within the limits of the family purse, there are those who, in the medical profession, lightly lend themselves to giving opinions that fit the case for a stipulated fee

Personally, my observation leads me to conclude that in this type of case the respectable mental expert does not sell himself as lightly as that To anyone acquainted, as doctor or lawyer, with the subject of psychiatry, the broad area of honest disagreement is so evident in a mass of border-line cases that it is not surprising that experts differ in these cases, with the result that there is what has sadly been referred to as the battle of experts

All this is complicated, too, by the confusion of uncertainty that arises out of what have been called metaphysical considerations in determining criminal responsibility by the use of the word "responsibility," itself, and the further use of the standard given to us in McNaughton's case of the ability to distinguish right from wrong

We have debated this test in legal circles, and it has been debated, too, as I know, in medical societies But, in this state at least, we have never budged an inch To criticize the doctor under these circumstances, because he differs with his colleagues when the courts are committed to the extent of this enormous area of medical choice is really pushing the thing too far To charge him, because of this, with selling his opinion, is most unfair

And, yet, frankness requires me to say that in my own experience, I have listened to startling testimony on the part of at least two most eminent psychiatrists, fanciful and puerile in their tests and their reasoning, and both on the side of the "big money" And I may add, too, that I was well acquainted with the writings of one of them, and not simply for purposes of the trial I had no difficulty in recognizing that he had woefully departed from reliance on the learning which he had passed on to me in the printed page

Nevertheless, I will say again that, generally speaking, I believe that the specialist in mental cases, of good professional standing, will not even for a substantial fee testify to what he cannot conscientiously support If nothing else, he values the good opinion and the good-will of

his scientific fellows. Primarily, however, it is because, fundamentally, he is an honest man.

I want to refer to my observation that doctors do not always like lawyers and the courts. I have tried to find out why. I cannot say that I blame them, but I do believe that if they made an effort and attempted to understand us, they would have fewer difficulties and fewer grievances. I may say, too, that the doctor who has a substantial experience with the courts finds less fault than do those whose judicial contacts are less frequent.

The conscientious, hard-working physician hates nothing worse, unless it be the loss of a patient's life, than the service of a subpoena. To him it means disruption of the routine of his practice, no matter what the need of patients who depend on him and his soothing presence. He usually must attend when it is most inconvenient and disturbing. But all doctors should be advised by their medical societies, and for that matter when they are being taught medical jurisprudence at school, that the doctor is the most favored of witnesses, even by opposing counsel, and usually by the court as well.

Rarely do lawyers and judges, if informed, compel him to wait. If he will ask for it, it can always be arranged that he be notified by telephone when he is about to be reached, and it happens time and again, when he comes to court in great distress, that he will be taken out of his regular order, heard, disposed of, and bundled off, to continue his good work of healing, medicating and cheering those who so greatly depend upon him.

The average medical witness dislikes a cross-examination that questions the correctness of his observations and the soundness of his opinions. To him, whose word is respectfully listened to in the sick room, it is a humiliation that a lawyer, who supposedly is nothing but an ignorant layman, should dare to take such an attitude.

When the inexperienced medical witness exhibits such a reaction, he is not very helpful. Just as the lawyer who is discourteous to the doctor in the court room loses the good-will of the jury, so, too, does the doctor fall in esteem when he is irritable, ill-tempered, uppish or opinionated.

The experienced medical witness makes no such mistake. He knows his advantage if he is denied the respect due to his position. He knows, too, that a cross-examination which is unsound carries within itself its

own undoing And, furthermore, he knows that the cross-examiner is not infrequently trained in this specialized type of work, has a sufficient accumulation of medical information to be able to conduct an examination intelligently and helpfully and probably is aided and guided by a physician who has studied the case and has competently advised the lawyer

In that connection, I might say that, notwithstanding the fact that many doctors think they have forgotten more than the lawyer will ever know, they often make a serious blunder There are many aspects of medicine with which many a physician is not thoroughly acquainted because such matters come within his ken only on rare occasions and because, too, he has not had as much schooling at the moment as the lawyer who examines him

For such situations, I can only make this suggestion, and I think it should be observed in all cases when a doctor testifies First, he should fully refresh his recollection concerning all of the facts observed by him, and then fully reflect on their significance medically, and then, too, take the pains to refer to a text here and there, as an additional help in sustaining his opinion in his mind, at least, and giving strength to a worthy cause Juries do not always accept a doctor's utterances on an *ipse dixit* theory

Now, there is another cause of irritation on the part of the experienced physician and that is the derision that greets his use of scientific words Again, experience avoids that difficulty The neophyte medical witness should remember that there are jurors who do not even understand the meaning of arteriosclerosis, that a thrombosis has about as much significance as a binary star, and that only a small fraction of them have ever heard the word "edema" They do not, in fact, know whether "sternum" is a heater or a breast-bone

To avoid court room titters, I suggest that plain English be used first, and the scientific term, if really necessary, be used later The jury will be so appreciative!

If the doctor will only ask the lawyer who calls him, and frankly confess his inexperience, the lawyer will be in a position, in good conscience, to be of service, and the expeditious judge, who presides over the trial, too, will be most grateful

There is another thing that doctors dislike in our courts, and that is the hypothetical question We can hardly blame them The patient

presented in the question is an unreal person. The recital from the doctor's viewpoint is incomplete and unreal, even when he participates in the preparation of the question. The doctor frequently objects to the requirement of a categorical "yes" or "no" answer, but wants to say more, and a lawyer will frequently shut him off with an objection.

Annoying and unsound as the hypothetical question is, it is the best the courts have been able to work out so far, and if the doctor is patient, and if there is a competent lawyer present in court, he will have an opportunity to explain fully his views, his reasons, and why he cannot scientifically and conscientiously answer "yes" or "no" in full truth. Judges always give people an opportunity to explain under such conditions even when they are not doctors.

I have observed that it frequently happens that defendants whose cases are conducted by insurance companies do not call medical witnesses. The reason, as I have found out, is that the company usually employs medical examiners who make reports. Because most of their cases are settled, it is desirable that the report be truthful and accurate. When the plaintiff's physician testifies to something in which the defendant's expert and medical investigator concurs, there is no point in the defendant's calling him and usually he is not called. In other words, medical testimony is not always disputed. This observation is confirmed by a statement made of record by an attorney for insurance companies concerning medical experts employed by plaintiffs, and as I would rather think well than ill of any group, I find the statement heartening and cheering.

I think I have given enough unsolicited advice and, I think, too, that I have expressed gratuitously enough opinions for the guidance of the members of another profession which is said to be almost as old as ours.

I shall presume no further, except to bespeak from both an interest in increasing numbers in the problems in the field of legal medicine which concern both, and a cooperation for improvement in the administration of justice in which the medical interest is at least as welcome and as useful as ours.

THE DOCTOR IN COURT*

CHAS GORDON HEYD

Professor of Surgery New York Post Graduate Medical School, Columbia University

"The constant and perpetual willingness to render each one his right"

FROM time immemorial the medical and legal professions have evolved along parallel lines. They arose in the dim past and each has had a distinguished history. Both were derived from the religious background of the Temple and probably had their first proponents as a doctor-priest and lawyer-priest. Simultaneously with the evolution of law and medicine, society progressed and civilization and culture became established in varying degrees in place and time. It may be said that the relative value of any period of civilization could be appraised by the character and development of these twin professions. Both medicine and law have been influenced, modified and changed by their social and political environment and today both stand an equal chance of being absorbed by the bureaucracy of government and liquidated as individualistic professions of public service.

It is an arresting fact that the study of law and medicine became formalized in Italy into an university status—law having its renaissance in the early part of the 12th century at Bologna and medicine at approximately the same time at Salerno. In the 820 years that have elapsed since the first university degree for lawyers and doctors was established, civilization has advanced and social relations have become so complicated that there has been evolved an extensive framework of laws, formulated and applied by professional experts.¹ It was inevitable that there should be a free intercourse in the development of legal procedures between the lawyers and the doctors, "for as long as litigants are represented in the court by trained lawyers insistence will be upon the rule of the law."² It would appear obvious that as long as patients are under the care of trained physicians there will be a legal insistence upon the use of scientific medicine, and as a corollary the law will recognize that

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only experts can qualify and testify upon that which is medically scientific, and in consonance with the general level of modern medical practice

A medical expert should be able to put the subject matter of his testimony as an expert in the form of a scientific essay, which, theoretically, he could present before any medical society. At the present time I have great doubts whether most of the experts would have the courage to do this and there are very few medical societies that would receive such a presentation.

The doctor, in the discharge of his professional duties, calls upon or receives his patients, asks questions, receives courteous replies and prescribes treatment by giving orders.³ The physician looks upon disease as a bodily disorder characterized by a lack of proper physiological function or a cellular disharmony and he attempts to reestablish orderly sequence of function. In brief, he applies a system of therapeutics to restore physical order. Subconsciously, the physician looks at the law as a system of legal therapeutics applied to a disordered society. In court, however, he finds himself placed in the witness box, takes orders not always courteous and is instructed to give categorical answers—"yes or no!"⁴ Instinctively, he feels that the court does not produce a harmonious remedy for social disabilities. Rightly or wrongly, he perhaps is disappointed or even grieved that his experience in court makes him believe that the application of the law is not a process of systematic or scientific social therapeutics but rather a compromise which permits the social body to function with many obvious maladjustments even though the essential cause of action is met by a relatively fair application of justice.

Medicine furthermore is not an exact or a finished science. It has none of the finality of geometry or calculus. In fact, the science of medicine will never be complete. Medicine is like an organism in having a growth, and must, in the nature of things, show variations with the progress of time, otherwise there would be no necessity for further research or investigation. The great biological essential for further progress in law and in medicine is for time and practice to evolve by normal growth, by trial and error, the logical development of both sciences. It would be a great detriment to society if in our zeal for reform we should cancel 800 years of social experience for the mere sake of change. Such unnatural haste might well delay further scientific development.

of the legal mind and impair the social consciousness of the community just as certainly as it would bar additional contributions to science and medicine. A system of law or medicine completely dominated and administered by government would likewise produce the same devastating result.

The economic situation⁵ that faces the legal profession is certainly worse than that which besets the medical profession. In every age and in every cultural order, the doctor has existed and maintained himself in spite of war, catastrophes and revolution. He lived and practiced his art during the decline and fall, or even the complete annihilation of previously existing states of civilization. From remote times the doctor has enjoyed complete professional freedom and has thereby assumed great social responsibility. In Russia the medical profession as such has survived even under a totalitarian government, although as a completely socialized system of medical practice.⁶

The doctor is part of the complex machinery of society and in his social obligations he is essentially a part of the government and his professional career many times brings him into intimate contact with the law. There are four ways in which the physician as a doctor appears in court: (1) as a plaintiff, as when he sues for non-payment for his professional services. In this particular role he may first have to defend a suit for malpractice before the way is clear for him to attempt to have legal settlement of an indebtedness due him, (2) as a defendant in malpractice action, (3) as a witness of fact, (4) as a medical expert witness.

The doctor as a witness of fact enjoys no more privileges than any witness of fact, and he is ordinarily required to give a frank statement without opinion as to what has come to his personal knowledge by contact with the patient. In most of the States, however, the doctor is subjected to "chiselling" by the plaintiff's lawyer from the practice that, as a witness of fact, the doctor is forced to become an opinion witness and is under the necessity of answering as a witness under the ordinary subpoena and does not receive remuneration for opinion testimony. In the State of New York, however, it is the practice that physicians may not be called upon to give opinions or to exercise the function of an expert without an agreement for compensation above the statutory fee for an ordinary witness. It is held by the New York Courts that a physician's knowledge is part of his occupation which no litigant has a right to use without proper compensation.³

Expert testimony and medical experts have been so thoroughly censured that when I attempt to defend the institution rather than the method I feel that I unconsciously become the representative of the great brood of experts. The way of a medical expert witness and the use of the hypothetical question is the *via dolorosa* for the doctor in court. Great has been the agitation and many have been the proposed reforms and practically every anathema and every form and type of vituperation have been evoked and hurled at the physician when he assumes the function of an expert. The expert, however, is permitted to express his opinion with respect to questions of science for it is held that the opinion of such persons who are especially skilled in such matters is a relative fact in the action.⁷

A story is told of a very prominent surgeon who had attained quite a reputation as an expert witness in negligence cases. He was glib of tongue and habitually exhibited an undue appreciation of his own value as a witness. On one occasion he was approached by a lawyer who anticipated bringing suit against a big corporation for alleged negligence. The doctor was asked if he would testify on behalf of the plaintiff. He said he would appear in court but he was too busy to go to the lawyer's office for rehearsals!

Learned Hand⁸ believes that the expert is an anomaly and, being a legal anomaly, serious practical difficulties arise, for "there can be no legal anomaly which does not work evil, because of forming an illogical precedent, it becomes the mother of other anomalies and breeds chaos in theory and finally in litigation." The chief objection of Judge Hand against expert testimony is that the expert becomes the hired champion of one side and is subject to examination, cross examination and contradiction by other experts. To obviate these objections the learned jurist recommends a "Board of Experts" and/or "a single expert," not called by either side, who shall advise the jury. Other suggestions have been made in regard to the question of expert testimony. These recommendations concern themselves with the mechanism or the technique of obtaining expert testimony but do not discuss the primary and essential need for expert testimony *per se*.

It has been suggested that the judge be allowed to call his own expert. This would seem to be a rather dubious procedure, for the doctor most intimate and confidentially close to the judge would probably be his family physician, who may or may not be a medical expert. The

second suggestion is that a panel of experts be created and from this panel either side and the court could select one, two or a reasonable number of experts for the purpose of testifying. This procedure is also of very doubtful value for it would create such a desire upon the more unethical members of the profession who, in the hopes of advertising or remuneration, would always be desirous of being placed on the panel. Such a panel would be open to all manner of political skullduggery and the panel would eventually arrogate to itself certain privileges and constitute in essence an extra-judicial body.

When we review the rules surrounding medical expert testimony together with the leniency of the court in regard to qualifying as an expert, it is apparent that almost any egotistically inclined physician may qualify as an expert. Furthermore, the expert is retained by either side and to that extent becomes a partisan in the final determination of the case. It would appear that the main defect of the expert medical witness in our courts is not that he is a medical expert witness but is our inability to be sure that he has special skill, knowledge and character. The point I wish to make is that our approach to the problem is not that the institution of the medical expert is fundamentally noxious or bad but at the present time there is no adequate mechanism for determining the competency of the expert as an expert. It would appear that in the solution of this difficulty lies the future of the medical expert testimony. The Court of Appeals in the case of *Szold vs. Outlet Embroidery Company* (274 N.Y. 271) unanimously upheld the position which prohibited the medical expert from recovering his fee for services rendered to an injured employee under the Workmen's Compensation Law until the doctor rendering the services had established his qualifications with the Workmen's Compensation Board conducted by the Medical Society of the State of New York. The Court of Appeals accepted the principle that the professional qualifications of a doctor may be established by the organized medical profession in a Workmen's Compensation case. This decision, undisturbed by the United States Supreme Court (March 1938), established a precedent for panels of experts whose qualifications have been established and approved by organized medicine.⁹

If we apply the principle formulated by this decision to the entire domain of medical expert testimony we have the mechanism for determining the character and competency of experts by non-governmental

bodies but within the framework of organized medicine

There are today fourteen special certifying boards working in collaboration with the Council on Medical Education and Hospitals of the American Medical Association. For example, the American Board of Surgery is a non-governmental agency, set up by various units of the medical profession where, by examination applicants are certified as to their competency in surgery. There are similar boards in medicine, in urology, in orthopedics, in psychiatry and neurosurgery, etc. Is it asking too much of any physician who offers testimony as a medical expert to be certified as to his qualifications in the special field in which he proposes to give his opinion?

There is a peculiar and devastating nomenclature about medical language that is difficult to translate into ordinary every day commonplace speech. While the doctor may use terms and words which convey a very definite meaning to his professional colleagues yet each individual expert will translate the same technical terms into a slightly different form of word and phrase of common language. In 1923 a patient engaged a surgeon to remove a tumor arising in the scar following an operation for appendicitis. The tumor was removed and the pathologist, a physician of great competency, reported that the tumor was a "fibroid tissue tumor with sarcomatous elements." The phrase "with sarcomatous elements" is definitely a diagnosis of one form of cancer. The patient was informed that the microscopical examination proved to be a "fibroid tissue tumor." The supplemental phrase "with sarcomatous elements" was withheld from the patient but conveyed to his father. About three years later the patient applied to an insurance company for a non-cancellable health and indemnity policy. He informed the company that he had been operated upon for a "fibroid tissue tumor," was duly examined by the company's physician, and accepted. For ten years he paid the annual premiums. The company then cancelled his policy because they claimed the insured had suppressed an essential statement "with sarcomatous elements" in his application. The patient sued the company to reinstate his policy. At the trial a prolonged controversy ensued as to the nature of "fibrous tissue tumors" and "sarcomatous elements." The attorney for the defendant added more complications by introducing an obsolete term called "desmoid" and seeking to buttress his position by an appeal to the "authority of a textbook." Five different experts were unable to explain to the jury in plain simple language just

what this tumor represented. Later, objectively viewing the testimony of the experts there was very little difference in the pattern of their testimony and all were in accord with the simple facts. If the tumor were a "fibroid tissue tumor," it was not cancer. If it were a sarcoma—cancer—the patient was cured. The jury found for the plaintiff. I have a definite impression that the effect of the experts' testimony is not always as impressive as some of our lawyers and doctors are inclined to believe. Twelve tried and true members of the community, sitting as a jury, will somehow arrive at a startling approximation of the truth regardless of the "scientific jargon" and controversies of the experts.

I wonder if it is always a good thing for society to have only experts. There are so many limitations to the expert in that his knowledge becomes so refined and his approach so circumscribed that he is very apt to have lost common touch with actual conditions. Is there not some reserve upon the part of the majority of persons against having experts determine everything for them? Is there not a sense of greater satisfaction to believe that ordinarily a jury will somehow approximate justice and fairness in their verdict? Certainly, it is true that technical facts can always be brought within the range of the intelligence of the jury.

The most outstanding question in the background of the medical expert is the relationship he bears to his profession. Few physicians reach positions of prominence in our hospitals without having professional merit and character, and as the truth of any individual's testimony is determined by his inherent honesty so the value of an expert's testimony is predicated upon the ethical relationship he bears to his profession. Therefore, medicine shares with the law the responsibility for guarding a great treasure—the ethical conduct of its practitioners.

The hypothetical question I am unable to discuss as it represents a terra incognita and I cannot offer anything to the extraordinary, voluminous literature that surrounds this question. I may, however, in passing make my salutations to this vexing question by recalling that I have read that the longest hypothetical question ever asked contained over 20,000 words and was submitted to Dr. Jelly of Boston, an expert on insanity. The question was propounded in the famous Tuckerman will case in Suffolk Probate Court. It concerned the testator's mental condition and required over three hours to propound. The answer of Dr. Jelly was startling! It was just three words: "I don't know."¹⁰

There is considerable misapprehension in the minds of the laity, no

less than the medical profession, that medical expert witnesses receive huge fees I am led to believe, both from my own personal experience and from conversation with other members of the profession, that the remuneration is on the whole inadequate

One of the most interesting stories associated with the remuneration of an expert is that which concerns the late Professor Henry Rowland. Some years ago an electrical concern in Buffalo engaged the Doctor, then Professor of Physics at Johns Hopkins University. Later on when the case had been finally disposed of there arose a disagreement about the fee for Professor Rowland's services. Subsequently he sued the company for \$10,000 for his services as an expert. The electrical company was represented by the late Joseph H. Choate. Mr. Choate's first question to the Professor was "Dr. Rowland, in your opinion who is the greatest physicist in America?" Without the slightest hesitation, Rowland replied "I am." Considerably later, Dr. Gilman, then President of Johns Hopkins University, playfully took Rowland to task for his lack of modesty on the witness stand. Rowland intimated to Gilman that he had failed to take into consideration the nature of his oath, that Rowland was to "tell the truth, the whole truth and nothing but the truth."

The value of the medical expert is, in the final analysis, determined by the character of men in medicine and in law, by their training and experience, by their certification by competent public bodies, by the social consciousness of the individual and by inherent traits of intellectual and personal honor. There will always be mendacious practitioners of law and medicine. Fundamental traits of character will not be changed overnight and I doubt if any lasting changes will be made or present procedure be greatly modified by hasty attempts at alleged reform. All social progress is based upon evolution and time is the element that brings the greatest benefit and acceleration to this process.

"Yet I doubt not thro' the ages one increasing purpose runs

And the thoughts of men are widened with the process of the suns."

Doctor Johnson asserted that "law is the science in which the greatest powers of the understanding are applied to the greatest number of facts" and "is the last result of human understanding acting upon human experience for the benefit of the public." I like to think of the law as I like to think of medicine, as permanent monuments to our civilization, as cathedrals of the human mind, exhibiting the best of all social progress through the centuries.

A few years ago I had occasion to visit the Cathedral at Chartres. It was in the late afternoon and the slowly descending sun illuminated the western skies with all the glowing colors of the spectrum. I seated myself in a sequestered niche and observed the mosaic of changing patterns as the diminishing light came through the celebrated Thirteenth Century windows. I was moved to reflect upon the vicissitudes of human affairs and of the common pact of society, a contract between the dead and the living, and those yet to be born. Seven hundred years were spent in the erection of this edifice and all of the members of the living society contributed to its creation, the banker, the money lender, the butcher, the baker, the humble dweller and the peasant. The work was apportioned according to the talents of the various contributors. It became an emblem and a symbol of the immortal spirit of humanity, it represented the continuity of life, its mutations, its physical and spiritual endeavors. It was at the same time, the glory and reverence of those that built it and those that used it. It was in fact the thread and imponderable spirit of a continuous force of the sublime aspirations of mankind. The individual contribution of each member of the community varied. Their talents were widely separate and disparate, their abilities uneven and their economic condition unequal. The whole edifice perished if the living violated their contract with the dead, yet each viewed the same monument with two eyes, saw the same thing and responded with the same spiritual evocations. They renewed their pledge and in doing so fulfilled the diurnal prayer of their lives. They became the continuous spirituality of an undefined soul. They recreated their hope and gave life to their inspiration. They were part of all that had been!

"Forerun thy peers, thy time, and let
Thy feet, millenniums hence be set
In midst of knowledge, dreamt not yet"

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LIBRARY NOTES

AN EXHIBITION OF BOOKS ON THE DISCOVERY OF VACCINATION, ITS EARLY ADVOCATES AND OPPONENTS

Prepared by

GERTRUDE L ANNAN

In Charge of the Rare Book and History Rooms

The volumes shown in this exhibition were selected from those on the shelves of the Academy Library. No attempt has been made to procure from other sources books which the Library does not possess. Thus, there are works not listed here which would obviously have been included in a selective bibliography. Only writings appearing during Jenner's lifetime have been considered, as limited space precluded any complete display of later publications.

WORKS BY EDWARD JENNER

Jenner, Edward 1749-1823

An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England and known by the name of the cow pox

London printed, for the author
1798

First edition of the author's work describing his discovery

Jenner, Edward 1749-1823

An inquiry into the causes

2 ed London printed for the author
1800, opened at pl opp p 30

Showing the hand of the dairymaid, Sarah Nelme, who was infected with the cow pox in May, 1796

Jenner, Edward 1749-1823

An inquiry into the causes

3 ed London printed for the author
1801, opened at pl opp p 34

Showing the arm of a five year old boy, inoculated March 16, 1798

Jenner, Edward 1749-1823

Further observations on the variolae vaccinae, or cow pox

London printed for the author 1799
This work was written, "to communicate such facts as have since occurred, and to point out the fallacious sources from whence a disease imitative of the true variolae vaccinae might arise, with the view of preventing those who may inoculate, from producing a spurious disease."

Jenner, Edward 1749-1823

A continuation of facts and observations relative to the variolae vaccinae, or cow pox

London printed, for the author
1800, opened at p 6

Jenner announces with satisfaction, "I have the pleasure too of seeing that the feeble efforts of a few individuals to depreciate the new practice, are sinking fast into contempt beneath the immense mass of evidence which has risen up in support

of it" He adds that, "upwards of six thousand persons have now been inoculated with the virus of cow pox, and the far greater part of them have since been inoculated with that of small pox, and exposed to its infection in every rational way that could be devised, without effect"

Jenner, Edward 1749-1823

The origin of the vaccine inoculation

London printed by D N Shury

1801

"I am induced to give the following concise history of the origin of vaccine inoculation, from my frequently observing that those who only consider the subject cursorily, confound the casual cow pox with the disease when excited by inoculation"

Jenner, Edward 1749-1823

Extract of a letter dated London, February 24, 1802

[London, 1802]

This contains "instructions for vaccine inoculation," with the warning "The most arduous task I have had to perform, has been making practitioners sensible of the absolute necessity of attending to the *quality* of the virus employed "

Jenner, Edward 1749-1823

[On modifications of the vaccine vesicle]

In *Medical and physical journal*, London, 1804, vol 12, p [97]

In this letter to the editor, Jenner explains that "herpetic affections which so frequently appear among the children of the poor often prevent the vaccine virus from producing its correct action" He believes this to be "the chief source of those failures, which many practitioners have witnessed in inoculating for the small-pox" This paper was later published separately

Jenner, Edward 1749-1823

Facts, for the most part unobserved, or not duly noticed, respecting variolous contagion

London printed by S Gosnell

1808, reprinted without alteration, 1811, opened at p [3]

"In my second and third treatises on the vaccine disease I endeavoured to call the attention of my readers to some physiological facts respecting the nature of the small-pox infection as the publica-

tions have been for some time out of print, and as the subject is by no means generally understood, I shall now make such extracts from them relating to this matter as I conceive may prove useful, and add some further observations "

Jenner, Edward 1749-1823

Letter to William Dillwyn, Esq on the effects of vaccination

[Philadelphia] published by the Philadelphia Vaccine Society 1818, opened at p [2]

The publishers state that this "communication was made in answer to the enquiry of one of our fellow citizens, who was desirous of knowing Dr Jenner's opinion of his truly interesting discovery, after it had stood the test of twenty years' experience. The friends of humanity will, no doubt, be highly gratified by this additional confirmation of the security to be obtained against the ravages of the small pox "

Jenner, Edward 1749-1823

Circular letter to the profession

In *Medico-chirurgical review*, London, 1821, vol 1 for 1820, p 780

A request to other physicians, asking them if the observations acquired in their practice coincided with those he had described in his earlier works

Jenner, Edward 1749-1823

[Facsimile of an autograph letter addressed to Sir Richard Phillips]

Cheltenham, January 16, 1807

In writing of the investigation of vaccination being carried on by the Royal College of Physicians, he says "This inquiry will lay all those troublesome ghosts which have so long haunted the metropolis with their *ox-faces*, & dismal hootings against vaccination you may depend upon it, the new investigation will prove the touch stone of the vaccine discovery "

Jenner, Edward 1749-1823

[Autograph letter addressed to William Clement, surgeon, of Shrewsbury, September 4th, 1811]

Cheltenham, September 4th, 1811

"It is now my wish to collect as many cases of secondary smallpox as I can find by application to my medical friends There are people in the world so absurd

as to suppose that cases of smallpox never occur either after inoculation or the disease taken in the ordinary way To con-

vince them to what an extent this has happened, is the purpose of an intended publication "

ENGLISH WORKS IN FAVOR OF VACCINATION, PUBLISHED DURING JENNER'S LIFETIME

Pearson, George. 1751-1828

An inquiry concerning the history of the cowpox, principally with a view to supersede and extinguish the small-pox

London printed for J Johnson 1798

The author was one of the first to recognize the value of Jenner's discovery and to experiment on a large scale. Subsequently, through his efforts a vaccine institution was founded This led to trouble with Jenner who was offered merely the post of extra corresponding physician, and who felt that Pearson was claiming a large part of the credit for the new discovery

Woodville, William 1752-1805

Reports of a series of inoculations for the variolae vaccinae, or cow-pox

London printed and sold by James Phillips and Son 1799

Like Pearson, Woodville, physician to the Small-pox and Inoculation Hospital, was quick to realize the importance of vaccination

Testimonial in favour of vaccine inoculation

In *London medical review*, 1800, vol 4, p 90

Signed by thirty-six eminent physicians and surgeons of London, this testifies that the signers believe it to be their duty to state their opinion, "that those persons who have had the cow-pox are perfectly secure from the infection of the small-pox, provided this infection has not been previously communicated" They state further that "the inoculated cow-pox is a much milder and safer disease than the inoculated small-pox"

Ring, John 1752-1821

A treatise on the cow-pox, containing the history of vaccine inoculation

London printed at the Philanthropic Reform 1801-3

One of a number of works by the author advocating vaccination It contains a careful summary of previously published

accounts of experiments made and conclusions drawn, by English and foreign physicians

Lettsom, John Coakley 1744-1815

Observations on the cow-pock

[London] printed by Nichols & Son

1801, opened at pl. opp p 3

The celebrated physician, Dr Lettsom, was a warm advocate of vaccination The plate shows a silhouette of Jenner Great Britain Parliament. House of Commons

Report from the Committee on Dr Jenner's petition, respecting his discovery of vaccine inoculation Ordered to be printed 6th May 1802

[London?, 1802]

"What his gains might probably have been, if he had been solicitous to keep the secret within his own practice may be collected from the testimonies in which no more than justice is done to the liberality and public spirit of the petitioner, in pursuing the propagation and extension of this important discovery, and in rendering it rather of universal utility than of emolument to himself"

This copy with Jenner's signature was presented by him to Dr Lettsom and from him it came to Dr Samuel L Mitchill of New York

Bloomfield, Robert. 1766-1823

Good tidings, or, news from the farm. A poem

London printed for Vernor and Hood 1804, opened at pp 18-19

This tribute to vaccination, was written by the shoemaker-poet

When the plain truth tradition seem'd to know,

And simply pointed to the harmless cow,
Doubt and distrust to reason might appeal,
But, when hope triumph'd, what did Jenner feel'

Appear'd the gift that conquers as it goes,
The dairy's boast, the simple, saving rose'

Momentous triumph—fiend! Thy reign is
 o'er,
 Thou, whose blind rage hath ravag'd ev'ry
 shore"

Bloomfield, pp 28-29, praises vaccination
 for preserving beauty from the ravages
 of smallpox

And is it then no conquest to insure
 Our lilies spotless and our roses pure?

Is it no triumph that the lovely face

Inherits every line of nature's grace?

That the sweet precincts of the laughing eye
 Dread no rude scars, no foul deformity."

Willan, Robert 1757-1812

On vaccine inoculation

London printed for Richard Phillips

1806, opened at p1 II

The distinguished dermatologist writes in
 his dedication, "I have endeavoured in the
 present publication, to rectify some mis-
 takes made by the first inoculators, to re-
 move several misconceptions, and to ren-
 der the practice of vaccination, more ac-
 curate and more secure"

Debates in Parliament respecting the Jen-
 nerian discovery, together with the re-
 port of the Royal College of Physicians of
 London on the vaccine inoculation

London printed by W Phillips

1808, opened at pp 140-141

The investigation of vaccination by the
 Royal College of Physicians was under-
 taken at the command of the King, in
 compliance with an address from the
 House of Commons The pages displayed

show some of the reasons for the Col-
 lege's support of the new practice.

Worgan, John Dawes 1791-1809

Select poems

London printed for Longman, Hurst,
 Rees, and Orme 1810, opened at
 p 205

This young poet was tutor to Jenner's
 children The verses shown are part of
 a poem entitled, "An address to the Royal
 Jennerian Society on their anniver-
 sary festival, May 17th, 1808"

'Tis thine, blest Jenner, with auspicious
 hand,

To chase one demon from the trembling
 land,—

Avert the fainting babe's impending doom,
 And rescue nations from the yawning tomb"

Carrick-Moore, James 1762-1860

The history and practice of vaccination

London printed for J Callow 1817,
 opened at p 300

The author served as Director of the Na-
 tional Vaccine Establishment after Jenner
 resigned in 1809 The conclusion of this
 early history of vaccination notes that
 "this is for the consideration of legisla-
 tors, who might in a very short time
 totally extinguish the small pox," and ends
 with the lines, "The discovery of Jenner,
 whose name, or, in strange tongues, a
 sound imitating his name, is now articu-
 lated through the world, in huts, houses,
 and palaces, a household word"

ENGLISH WORKS OPPOSING VACCINATION, PUBLISHED IN JENNER'S LIFETIME

Moseley, Benjamin 1742-1819

Medical tracts I On sugar II On the
 cow-pox

2 ed with considerable additions Lon-
 don printed by John Nichols

MDCCC, opened at p 180

First published in 1799, this tract came
 from the pen of one of the foremost op-
 ponents of vaccination He writes "Great
 events are foreboded—Some pretend that
 a restive greasy-heeled horse will kick
 down all the old gally-pots of Galen—
 Others, that the people of England are
 becoming like the inhabitants of a wilder-

ness seen in 1333, by Sir John
 Mandeville,—who, he says, were "wild, with
 horns on their heads, very hideous and
 speak not, but rout as swine."

A new song, to the tune "And a begging
 we will go" Inscribed to the great Dr
 Jenner

[London?, 180?]

"Minitt, the cowleech instructor of
 Jenner on the cow-pox" is quoted

"I minds my cows and horses, I tells you all
 I know,

You writes a book about it, you speaks of
 horse and cow,

While a begging you do go
How comes it Maister Jenner, that you're
doctor call'd,
When you kept shop at Berkeley, and me
horse med'cines sold,
Ere a begging you did go"

Lipscomb, George 1773-1846

A dissertation on the failure and mischiefs
of the disease called the cow-pox in which
the principal arguments adduced in fa-
vour of vaccination are examined, and
confuted

London printed for George Robinson
1805

The distinguished historian, surgeon and
physician concludes his observations with
the statement that "vaccination ought to
be immediately, and for ever, abandoned"

Rowley, William 1742-1806

Cow-pox inoculation no security against
small-pox infection to which are add-
ed, the modes of treating the beastly new
diseases produced from cow pox

3 ed London printed, for the author
1806 opened at pl opp p [v]

A tirade against vaccination showing a
plate entitled, "cow poxed, ox-faced boy"

Stuart, Ferdinand Smyth fl ca 1800

£80,000 for the cow-pox'!! An address
to the British Parliament, on vacci-
nation wherein the report of the
College of Physicians is completely con-
futed

2 ed London sold by Hatchard
1807, opened at pl opp p 61

The author, a physician of Billericay, Es-
sex, claims to have practised for thirty-
five years, as well as serving as a Major
in the army. The plate is the familiar
illustration showing babies being shoved
into a monster's mouth while the opposers
of vaccination stand in the background,
their swords drawn in their fight for
truth. Stuart, who lost his infant son
through vaccination, describes the fate of
a child who, having been vaccinated, "ran
upon all fours like a beast, bellowing like
a cow, and butting with its head like a
bull"

Moseley, Benjamin 1742-1819

An Oliver for a Rowland or, a cow pox
epistle

10 ed with considerable additions Lon-

don sold by Longman, Hurst, Rees, and
Orme 1807, opened at p 61

Another of the many tracts by Moseley
against vaccination. This scurrilous at-
tack on Rowland Hill, who championed
vaccination, is typical of the virulent
pamphlets written by both his followers
and his opponents. Its popularity is evi-
denced by the number of editions which
were published after the first appeared
in 1806. As a mild example of Mose-
ley's invective are these lines in the Ap-
pendix: "So, Rowland, since the fourth
edition of my Oliver, you have sunk down
among the swine-pox herd, in Dr Brad-
ley's yellow pigsty there you may
wallow and grunt, and play the swine with
the brute creation"

Birch, John 1745-1815

A copy of the answer to the queries of
the London College of Surgeons, and of
a letter to the College of Physicians, re-
specting the experiment of cow-pox
to which is added, the second edition of
serious reasons for objecting to the
practice of vaccination

London printed by J Smeeton 1807

One of a number of articles by the well
known surgeon who was an ardent foe
of vaccination. He writes that the Col-
lege of Physicians "were not authorized to
draw any conclusions in favour of vac-
cination from the facts before them". The
title-page has the inscription "For Dr
Moseley from the author"

Metallic tractors, and cow pox inoculation
On Thursday, June 11, 1807, at the British
Forum. Question "Which has proved
a more striking instance of public credulity,
the metallic tractors of Perkins—or the cow
pox inoculation?"

[London?, 1807]

"The mask of deception, at length, is al-
most removed, and many of those who
formerly countenanced these absurdities,
now repent of their folly, and resent the
imposition practised upon their under-
standings"

Adjourned debate. Metallic tractors, and
cow pox inoculation. On Thursday, June
18, 1807, at the British Forum

[London?, 1807]

"After an interesting discussion, before

a numerous and intelligent audience, (among whom were several persons of the first eminence in the medical profession) the farther consideration of the question was adjourned "

Cow-pox

In *Cobbett's weekly political register*, London, vol 13, June 18, 1808, col 965-967

"This experiment, which has cost the nation twenty thousand pounds, or more, to Dr Jenner, is now, it seems, to have an

act of Parliament to give it currency Mr Rose has brought in a bill for the purpose of 'establishing a central institution in London for the distribution of the cow-pox matter ' and thus this disgusting and degrading remedy will cost the nation another four or five thousand pounds annually " William Cobbett, 1762-1835, the famous controversialist, uses his journal for this attack on vaccination

THE SPREAD OF VACCINATION TO FOREIGN COUNTRIES

FRANCE

Desoteux, François 1724-1803, and Valentin, Louis 1758-1829

Traité historique et pratique de l'inoculation

A Paris chez Agasse Fuchs
l'an 8 [1800], opened at pp 302-303, foot-note

In this treatise on inoculation the authors bring to the attention of the French a brief account of Jenner's work, with the information that ample details may be found in articles published in the *Bibliothèque britannique*, nos 69-72, 1798-9 A French edition of Jenner's work was published in Lyon in 1800

Woodville, William 1752-1805

Rapport sur le cowpox ou la petite vérole des vaches, et sur l'inoculation de cette maladie ouvrage traduit de l'Anglais, augmenté d'un précis de ce qui a été fait sur cette maladie, et de notes historiques par A Aubert, D M

A Paris chez l'Auteur Gabon

J A Brosseau an VIII [1800]

A translation of Woodville's tract by Antoine Aubert, 1772-1820, eminent Swiss physician who worked under Woodville in London

Colon, François 1764-1812

Histoire de l'introduction et des progrès de la vaccine en France

A Paris chez le Normant an IX — 1801, opened at a₁

Colon was one of the first and most ardent advocates of vaccination in France "Pères et mères, je ne pouvois vous don-

ner des preuves plus convaincantes de la bonté de la vaccine, qu'en étant le premier à Paris qui l'aie employée pour son enfant "

Husson, Henri Marie 1772-1853

Recherches historiques et médicales sur la vaccine

2 ed augmentée a Paris chez Gabon et cie (1801), opened at p 132

Another early enthusiast in France writes, "la Postérité bénira la mémoire de Jenner, et les siècles à venir le proclameront l'un des premiers bienfaiteurs de l'humanité"

Moreau, Jacques Louis 1771-1826

Traité historique et pratique de la vaccine

A Paris chez Bernard (1801), opened at p 346

Moreau, a medical librarian and historian of medicine predicts that vaccination will make smallpox vanish from the earth

Comité Central de Vaccine

Rapport du Comité

A Paris de l'imprimerie de Guillenot, chez Mme Ve Richard 1803, opened at p ix

A group of French citizens formed in 1800 a society to investigate the new discovery The Committee appointed to carry out the investigations, after three years' consideration, concluded "Les essais les plus multipliés, les épreuves les plus décisives, les autorités les plus imposantes, une approbation unanime et générale dans toute la France comme dans tout l'univers médical, ont dissipé les doutes, amène la con-

viction, et forcé au silence ceux même des adversaires que l'évidence n'a pas convertis"

Chappon, Pierre. 1749-1810
 Traité historique des dangers de la vaccine, suivi d'observations sur le rapport du Comité Central de Vaccine
 A Paris chez Demonville et Soeurs
 1803, opened at p 268

The author, a violent opponent of vaccination, maintains that "Le Comité Central de Vaccine de Paris, loin d'affaiblir mes opinions, les a singulièrement fortifiées par ses très-faibles et très-insignifiantes refutations des faits énoncés par les

antagonistes de ce moderne spécifique "

Gauthier-Désiles, Antoine Marie fl ca 1800
 La vaccine, poeme
 A Paris chez Michaud frères et chez P Blanchard et Ce. M DCCC
 X, opened at p 27

"Salut au bon Jenner, bienfaiteur des mortels'
 Leurs coeurs reconnaissants lui doivent des autels
 Lui seul, dans nos climats que désole la guerre,
 Sait réparer les maux causés par l'Angleterre."

GERMANY

Jenner, Edward 1749-1823
 Untersuchungen über die Ursachen und Wirkungen der Kuhpocken aus dem Englischen übersetzt von G Fr Ballhorn
 Hannover bei den Gebrüdern Hahn, 1799
 This German edition of Jenner's work was translated by the physician, Georg Friedrich Ballhorn

Pearson, George 1751-1828
 Untersuchung über die Geschichte der Kuhpocken aus dem Englischen übersetzt von J F Küttlinger
 Nürnberg in der Raspeschen Buchhandlung, 1800
 A translation into German of Pearson's work by the physician, Johann Küttlinger, 1778-1851

Aikin, Charles Rochemont 1775-1847
 Kurzgefasste Übersicht der wichtigsten Thatsachen welche bisher über die Kuhpocken erschienen sind Aus dem Englischen übersetzt von J Hunnemann
 Hannover bei den Gebrüdern Hahn, 1801
 A German translation of the work of the physician and chemist The English edition was published in 1800

Schmidtgen, J G D fl ca 1800
 Die Kuhpockenimpfung in Briefen an Sophie M*** geb T***

Leipzig bei Wilhelm Rein, 1801, opened at pl at end

The author calls himself the Director of the Almshouse, but says he is writing as a citizen of the world rather than as a physician He says, "Zur Herausgabe dieser Briefe wurde ich durch einige mir sehr schatzbare Männer veranlasst, und mein Herz war um so bereitwilliger dazu, da ihr Gegenstand so gemeinnützig ist "

Kühn, Karl Gottlob 1754-1840
 De morbo vaccino-variolo super quibus A D XXXI Jul CIOCCCCI publice disputabit Carolus Gottlob Kühn adsumto socio Christiano Samuele Weiss
 Lipsiae impressit Joannes Gottlob Henricus Richter, [1801]
 The distinguished historian of medicine advocates vaccination

Wetzler, Johann Evangelist. 1774-1850
 Gedanken über die beste Art und Weise, die Impfung der Kuhpocken
 München im Verlage bey Johann Esaias Seidel, 1803, opened at p [7]
 The Director of the Vaccination Institute at Ulm writes "Durch allgemeine Impfung der Kuhpocken ist in der künftigen Generation die Bevölkerung in Europa wenigstens um 15 Millionen, in Teutschland um 2 Millionen, in Baiern um 200000 Menschen vermehrt "

ITALY

Raccolta di memorie di osservazioni ed esperienze sopra l'inoculazione della vaccina o sia vajuolo delle vacche a preservazione della umana specie traduzione dal Francese

Venezia dalle stampe di Giovanni Zatta, 1801, opened at p 18

This collection contains among other items a translation of an article of Odier's published originally in the *Bibliothèque britannique*, Geneva, nos 113 and 114 Louis Odier, 1748-1817, was an early advocate of vaccination in Geneva

Barbieri, Matteo fl ca 1800

La vaccina alla prova ossia l'antiperistasi del vajuolo memoria

Verona presso l'Erede Merlo, 1802, opened at p 147

The list of persons vaccinated in Verona in 1801 which starts on page 147 includes 160 cases

Cisalpine Republic Risultati di osservazioni e sperienze sull'inoculazione del vajuolo vaccino instituite nello spedal maggiore di Milano dalla Commissione Medico-Chirurgica superiormente delegata a questo oggetto Pubblicati per decreto del Comitato Governativo della Repubblica Cisalpina

Milano dalla tipografia di Luigi Veladini, anno X [1802], opened at p 223

The Committee's experiments led to the conclusion that there were no important objections to vaccination, but the Committee felt that the satires against vaccination "in materia tanto grave e importante, sono ancora una prova della mancanza di argomenti solidi e reali"

Calcagni, Francesco fl ca 1800

A letter on the inoculation of the vaccina, practised in Sicily translated from

the Italian by Edward Cutbush

Philadelphia published by B and T Kite 1807, opened at p 8

"Sicily is indebted, for the introduction of the vaccina to the care of Civ Sig D Giovanni Vivenzio, and Sig Michele Troja, well known for their literary works, on medicine and surgery The first vaccination, in Palermo, was performed by Jos H Marshall, March 14th, 1801 The continuance of it in Palermo was not owing to my attention and labour only, but to the diligence and care of D Ciro Troja" Cutbush, 1772-1843, was a surgeon of the United States Navy

Sacco, Luigi 1769-1836

Trattato di vaccinazione con osservazioni sul giavardo e vajuolo pecorino

Milano dalla tipografia Musc, MDCCCIX, opened at p 6

Sacco was responsible for the introduction of vaccination into Italy and was one of its most ardent supporters He writes that he himself vaccinated more than 500,000 individuals, while 900,000 others were vaccinated by men appointed by him for that purpose.

Ponta, Gioachino fl ca 1800

Il trionfo della vaccina poema

Parma co'tipi Bodoniani, MDCCCX, opened at p 1

'Canto l'arabo morbo, e i duri mali,

Con che l'umanità tremendo afflisce,

E l'arte che a domarne il toscio e l'ali

Invano sudd tanto e tanto scrisse

E la tarda pietà degl'immortali

Che alfin Jenner credè, che lo sconfisse,

E i suoi seguaci e i re propizj io canto,

Onde cessò d'umanità il pianto"

OTHER COUNTRIES

de Carro, Jean 1770-1856

Beobachtungen und Erfahrungen über die Impfung der Kuhpocke aus dem Französischen übersetzt von Joseph von Portenschlag

Wien in Joseph Geistinger's Buchhandlung, 1802

The author, a native of Geneva, practised medicine in Vienna, and was instrumental in the spread of vaccination

von Portenschlag-Ledermayer, Joseph 1742-1834

Über den Wasserkopf nebst einem Anhang und einen Aufsatz über die Kuhpocke enthaltend

Wien gedruckt und verlegt bey Anton Strauss, 1812, opened at p 545

This Viennese physician writes 'Ich habe seit acht Jahren 1270 Personen vacciniert, darunter einige wenige erwachsen waren,

und niemahls habe ich gefährliche Folgen beobachtet "

[Description of the expedition of Francisco Xavier de Balmis & Berenguer executed with the sole object of carrying to all the possessions of the Crown of Spain, situated beyond the seas, the estimable gift of vaccine inoculation]

[Cheltenham, 1806]

This is a translation of the Supplement to the *Madrid gazette* of October 14th, 1806 De Balmis, surgeon to the King, sailed in November, 1803 The expedition was divided into two sections, one which went to South America, the other to Havana and thence to Yucatan, Mexico, etc De Balmis, sailing as far as China, did not return home until August, 1806 This volume with both the Spanish and English text, has an inscription on the fly-leaf "With Dr Jenner's best wishes Cheltenham, Dec 21, 1806"

Hernandez, Rafael 1779-1857

Observaciones-historicas del origen, progreso y estado actual de la vacuna en Menorca

Mahon imprenta de Fabregues, 1814, opened at p 28

The author of this favorable account of vaccination in Minorca writes "Pero afortunadamente los mas se convencieron y penetraron de que era dimanado de haber tenido los indicados la vacuna espurea prueba irrefragable de ésta luminosa verdad, es haber permitido en aquella lamentable crisis variolosa, que sus tiernos hijos fuesen vacunados con el mas feliz y dicho exito "

de Araujo Carneiro, Heliodoro Jacinto ff ca 1800

Reflexões, e observações, sobre a pratica da inoculação da vaccina, e as suas funestas consequencias feitas em Inglaterra

Londres na impresao de Mr Cox, Filho, e Bavlis 1808, opened at p 111

The author describes himself as physician to His Royal Highness, Prince Regent of Portugal An English translation appeared in 1809 This copy was a gift from the author to Dr Moseley A translation of the passage shown above reads "Probably many infants have descended to their graves the victims of the obstinacy of those who wilfully persist in their error and delusion But a day will come when the healing art will be again rendered mystic and religious, to avoid the abuse of men's imagination"

Keir, George d after 1814

Account of the introduction of the cow pox into India

Bombay printed by Moroba Damotherjee 1803

"The following account of the successful introduction of the vaccine disease into Bombay, and its diffusion throughout India, is inscribed to Jonathan Duncan, to whose interposition, the Indian world are indebted for the blessings that have already marked the progress of vaccination, as well as for the incalculable benefits that must arise from it, to every quarter of the British Dominions in Asia' Keir was a surgeon in the Indian medical service. Duncan was Governor of Bombay

THE SPREAD OF VACCINATION IN THE UNITED STATES

The following important account of a new publication in Great-Britain, by Dr Jenner, entitled "An inquiry into the causes and effects of the variolae vaccinae, or cow pox," is extracted from the *Analytical Review* for July, 1798

In *Medical repository*, N Y, 1799, vol 2, p 255

An early and favorable report of the discovery

Waterhouse, Benjamin 1754-1846

A prospect of exterminating the small

pox being the history of the variolae vaccinae, or kine-pox, commonly called the cow-pox with an account of a series of inoculations performed for the kine-pox, in Massachusetts

[Cambridge] printed for the author, at the Cambridge press, by William Hildhard 1800 opened at p 18

An account of the first vaccination performed in the United States

[Print, comparing appearance of vaccine vesicles with those caused by inoculation of

smallpox This is an original print sent by Jenner to Waterhouse in 1801]

North, Elisha 1771-1843

A treatise on a malignant epidemic, commonly called spotted fever

New-York printed and sold by T & J Swords 1811, opened at p 2, footnote

In this notable work, the first volume on cerebrospinal meningitis, the author writes, "I obtained some vaccine infection from New-Haven in December, 1800, which matter came from Dr Waterhouse This was, I believe, the first matter which proved to be genuine that was ever used west and south of Connecticut River This acquisition enabled me to become acquainted with the cow-pox during the winter" In May, 1801, a young man consulted him, who, upon examination, proved to be suffering from the kine-pox, the first example of the disease to be recognized in this country

Jefferson, Thomas 1743-1826

[Autograph letter signed, addressed to Dr John Shore Photostat copy of original in the Massachusetts Historical Society]

Monticello, September 12, 1801

On December 1, 1800, Waterhouse wrote to Jefferson, sending him a copy of his work on vaccination Jefferson, interested in the new discovery, replied promptly and gave his whole hearted support. In this letter, less than a year later, he writes, "I received about a month ago some vaccine matter from Dr Waterhouse at Boston, and by a second conveyance some which he had just received from Doctr Jenner of London Both have succeeded perfectly" In a letter to Waterhouse, July 25, 1801, Jefferson had informed him that both the first and second supplies of "vaccine matter had failed"

Seaman, Valentine 1765-1817

A report on the vaccine or kine-pox inoculation in New-York

In *Medical repository*, N Y, 1802, vol 5, p 236

"With infection fresh from the arm of Governor Sergeant's domestic, who had been inoculated in Boston by Dr Waterhouse, and who arrived here on the 22d of

5th month (May) [1801], in due season for his pustule to contain active matter, I succeeded in vaccinating a number of persons, in this city The complaint left no doubt on my mind of its being the genuine vaccine disease."

Seaman, Valentine. 1765-1817

An account of the introduction of vaccination or kine-pock inoculation in New-York [Manuscript in the hand of the author]

[New York, 1802], opened at p [18] Seaman in this manuscript quotes a number of brief articles written by himself and others The *Mercantile Advertiser*, New York newspaper which published several notices concerning the new discovery, printed, December 30th, 1801, an extract of a letter from Seaman to Waterhouse, dated December, 22d, 1801 In this letter Seaman complains of the opposition of New York physicians to vaccination, "Indeed such a general apathy seems to pervade the minds of even of those who certainly must be convinced of its advantages, that I have not yet got a single co-operator among them "

Cove, John Redman 1773-1864

Practical observations on vaccination or inoculation for the cow-pock

Philadelphia printed and sold by James Humphreys 1802, opened at pp 122-3

Cove, through Dr John Vaughan, communicated with Jefferson The latter's reply, "together with the vaccine infection, was received on the 9th of November, 1801, a day which I trust will be memorable among the citizens of Philadelphia, from the great benefit connected with it I immediately employed the infection on myself and four others "

Jenner, Edward 1749-1823

An inquiry into the causes and effects of the variolae vaccinae from the second London edition

Springfield re-printed for Dr Samuel Cooley, by Ashley & Brewer, 1802, opened at pl opp p 22

American edition of Jenner's work

Ramsay, David 1749-1815

The Charleston medical register, for the year M DCCCII

Charleston printed by W P Young
1803, opened at p 5

"Vaccination was introduced into Charleston, in February, and in a short time became general. Nothing is now wanting to exterminate the small-pox, but a general and simultaneous vaccination." In his *History of South Carolina* Newberry, S C, 1858, vol 2, p 45, he writes "This substitute for the small pox was introduced into Charlestown by David Ramsay, who after many trials succeeded in February, 1802, in communicating the disease to his son Nathaniel."

Waterhouse, Benjamin 1754-1846

A prospect of exterminating the small pox Part II, being a continuation of a narrative of facts concerning the progress of the new inoculation in America, together with practical observations on the local appearance, symptoms, and mode of treating the variola vaccina, or kine pox including some letters to the author, from distinguished characters, on the subject of this benign remedy

Cambridge printed for the author, at the University press by William Hilliard, 1802 opened at p 113

Part of a letter from Jenner to Waterhouse is shown here, containing Jenner's rules, which he believes "should be perfectly understood by those who practise the vaccine inoculation."

Massachusetts Medical Society

Report on vaccination, read June 1, 1808

In *Medical communications of the Massachusetts Medical Society*, Boston, published by the Society, 1808, vol 1, no 2, part 2, opened at p 137

A committee appointed to investigate vaccination made the following resolutions

First—That persons who undergo the cowpock are thereby rendered as incapable of being affected by the virus of smallpox

Second—That in the early and even in some of the late practice of inoculating for the cowpock, the disease may not have been produced in the most perfect manner

Third—That the most perfect and absolute security is to be derived from sub-

sequent inoculation

Fourth—That it be recommended that all persons who have been vaccinated call on those who inoculated them to perform a second inoculation."

[Certificate testifying that] "The twelve individuals whose names are written on the back of this card were vaccinated by Doctor Amos Holbrook at the town inoculation in July last, they were tested by small pox inoculation on the 10th instant, and discharged this day from the hospital after offering to the world an additional proof of the never failing power of that mild preventive, the cow pox against small pox infection."

Milton, October 25th, 1809

A collection of papers relative to the transactions of the town of Milton, in the state of Massachusetts, to promote a general inoculation of the cow pox, or kine pox, as a never failing preventive against small pox infection

Boston printed for the town of Milton, by J Belcher, 1809, opened at p 11

The Selectmen of the town of Milton called a special meeting to consider "adopting some measures for a general inoculation of the cow pox." The town was divided into districts and the offer made to "inoculate any of the inhabitants of said town for twenty five cents each." "In the course of a few days it was completed, offering for a result three hundred and thirty-seven individuals inoculated." The Selectmen advise, "the institution in every town—of public measures—of a yearly inoculation—of a register—and of a standing committee of active zealous men."

Waterhouse, Benjamin 1754-1846

Information respecting the origin, progress, and efficacy of the kine pox inoculation extracted from "A prospect of exterminating the small-pox"

Cambridge printed by Hilliard and Metcalf, 1810, opened at p 53

Although the author's experiments with vaccination, and particularly his insistence on the use of vaccine virus of pure quality, his wide correspondence and his publications, established his reputation as a scientist, his personal animosities made

him fervently disliked by his colleagues, and led to his being ousted from the university. He presented a petition to the Legislature of Massachusetts asking for remuneration for his services. Marginal notes in this copy, which seem to be written in his hand, refer to the refusal of his request. "Party politics defeated his application. Congress treated his petition with respect, & a committee reported that he should be recommended to the President. In consequence Dr W was offered the place of hospital surgeon, with his locality fixed where he now resides. Soon after this the outrageous spirit of party, we at that time, marked and disgraced Massachusetts, stripped him of all his offices in the university, leaving him now nothing for the support of his large family, the pay & rations of an hospital surgeon—grey hairs & want of bread." Another in-

scription in the same hand is dated, Cambridge, Janv 15th, 1817
Seaman, Valentine 1765-1817

A discourse upon vaccination

New-York printed and sold by Samuel Wood & Sons 1816, opened at p [5]

In this lecture to students at the New York Hospital, Seaman says, "You have now, in a variety of cases, witnessed an operation, which, although the most simple and trifling of any that comes under the hand of a surgeon, is, in its consequences, of the greatest importance. It has probably already done more good to society, prevented more pain and distress, and preserved more lives, than *all* the capital operations that have ever been performed." He explains that "All children born in the lying-in-ward of the hospital, are vaccinated before they leave the house."

VACCINE INSTITUTES

London Vaccine Institution

Plan and regulations of the London Vaccine Institution, for inoculating and supplying matter, free of expence

[London] J Swan, printer [1808]

This organization was formed in 1806, with John Walker, 1759-1830, as Director. Walker had served as Resident Inoculator of the Jennerian Society which was founded in 1803, but was forced to resign. With friends, he then started this new organization.

London Vaccine Institution

At the Annual Meeting of the Governors holden April 6th, 1809 Report

London printed by Darton and Harvey [1809]

The Board reports that the number of vaccinations done since the organization was begun, are 4,018 by Dr Walker, 2,921 by "appointed inoculators in the Metropolis," and 102,008 by the "appointed inoculators in the country."

Vaccine Pock Institution

The report on the cow-pock inoculation, from the practice at the Vaccine-Pock In-

stitution, during the years 1800, 1801, and 1802

London printed and sold by Henry Revnell 1803, opened at p 127

This Institution was founded in 1799 by Pearson, and led to trouble between Pearson and Jenner. Inserted at p 127 of this report is a folding chart, entitled, "Formula of the register sheets of the Vaccine Institution."

Vaccine Pock Institution

Directions for the vaccine inoculation

[London] printed by Henry Revnell, [1804]

"The Institution does not warrant any matter but that which has on the package, the impression of the seal of the Institution, *namely*, a cow, with the motto, *Feliciores inserit*"

National Vaccine Establishment.

The Board appointed by His Majesty's Government to regulate the affairs of this Establishment is composed of the President and four Censors of the Royal College of Physicians, the Master and two Governors of the Royal College of Surgeons. Ordered by the Board that the following description of the vaccine

vesicle and instructions relative to vaccination be strictly observed

[London] J Smeeton, printer

[1809], opened at p 3

This organization, sponsored by the Government, was founded in 1808 This copy has annotations in the hand of John Birch, opponent of vaccination, dated November 5th, 1809 "Dr Jenner has since deserted his friends at the Vaccine Establishment, has run away from London and dares not go to Cheltenham, because the smallpox has broke out in several patients vaccinated by himself, and because it is proved that he has inoculated his own child with *smallpox*, not daring to trust his own experiment as a security"

Royal Jennerian Society

[Engraved diploma, presented to Dr James Anderson, 1798-1886, of New York, on his election as Honorary Member, London, May 17th, 1820]

London Vaccine Institution

[Engraved diploma presented to Dr James Anderson in testimony of the high value placed on "his liberal cooperation in the philanthropic cause of vaccination," February 28th, 1821]

These two organizations had been previously united with Dr Walker as Director

New York Institution for the Inoculation of the Kine Pock

[Minutes of meetings]

[New York, 1802-1805], opened at fo 1r-2r

These pages show the Minutes of the meetings held on April 22, 1802 and May 20, 1802 The Minutes of the earlier meeting announce, that "The Committee appointed to represent the objects of the Institution to the corporation of this city, & request that the poor children of the Almshouse might be inoculated under its directions—reported, that the Common Council at their last meeting had not come to a decision thereon"

New York Institution for the Inoculation of the Kine Pock

Constitution for the government of to which are added, the Proceedings of the two first meetings of the Contributors
New-York printed by Isaac Collins and Son, 1802 opened at p [3]

"A number of citizens of New-York, convinced of the important advantages to be derived from substituting the kine pock in place of the small-pox inoculation, in this country, have associated for the promotion thereof, and liberally contributed towards the establishment of an institution for the purpose of disseminating the benefits of this new inoculation among the poor, of supporting a constant supply of the genuine infection, and of promoting a more general knowledge of the disease, and the proper method of successfully communicating it "

New York Institution for the Inoculation of the Kine Pock

Facts and observations relative to the kine-pock Addressed to the more indigent part of the community

New-York printed by Isaac Collins and Son, 1802, opened at pp 6-7

"A number of benevolent citizens have associated and established a permanent institution, a main object whereof is to disseminate the blessings of this disease, free of cost, among the indigent members of the community "

New York Institution for the Inoculation of the Kine Pock

Directions for the kine pock inoculation

[New York, 1802], opened at p [3]

The signatures of the members of the Medical Board, consisting of Valentine Seaman, Edward Miller, and Samuel Borrowe, appear at the end of these directions, followed by some resolutions made by the Directors concerning the supplying of matter for inoculation to physicians

Smith, James 1771-1841

Prospectus of a permanent national vaccine institution, to be established in the city of Washington, District of Columbia.

Baltimore, 1818, opened at p [3]

Smith performed vaccinations in Maryland as early as May, 1801 He persuaded the Legislature of Maryland to enact a law for the establishment of a vaccine institute in 1809 Although his efforts to found a national vaccine institute failed, he directed the United States Vaccine Agency which was in existence from 1813 to 1822

VACCINATION IN CARICATURE

Aesculape, revue mensuelle illustree

Paris, 1912, vol 2, opened at pp 138-139

Burroughs Wellcome & Company

The history of inoculation and vaccination

London, [1913], opened at p [106]

Der Arzt in der Karikatur herausgegeben von Cornelis Veth mit einer Einleitung von Friedrich Krauss

Berlin Otto Stollberg, [1928-], opened at p 55

Cabanès, Augustin 1862-1928

La medecine en caricature

Paris P Longuet, [1925], opened at p [11]

Hollander, Eugen 1867-1932

Die Karikatur und Satire in der Medizin

Stuttgart Ferdinand Enke, 1905, opened at p [305]

Hollander, Eugen 1867-1932

Die Karikatur und Satire in der Medizin

2 ed Stuttgart Ferdinand Enke, 1921, opened at p [351]

I N F E C T I O N S

A THREE-FOOT SHELF FOR THE PRACTITIONER

Selected by

FRANK PLACE

Chief Reference Librarian

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Chicago, Year Book Pub [1938], 149 p

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Springfield, Ill, C C Thomas, 1935, 581 p

Goodall, J R Puerperal infection Montreal, 1932, 189 p

Great Britain Med Research Council Diphtheria, its bacteriology, pathology and immunology London, H M S O, 1923 544 p

Greenwood, Major Epidemics and crowd-diseases An introduction to the study of epidemiology London, Williams & Norgate, [1935], 409 p

Hammond, T E Infections of the urinary tract. London, H K Lewis Co, 1935, 250 p

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7 ed Phil, Lea & Febiger, 1939, 503 p

Libman, Emanuel General infections by bacteria In New York Academy of Medicine Lectures on medicine & surgery, 1927, pp 69-91

Libman, Emanuel & Friedberg, C K Bacterial endocarditis In Cyclopedia of Medicine (Piersol) 2 ed, Phil, F A Davis Co, 1939, v 3, pp 648-665

MacNevin, M G & Vaughan, H S Mouth infections and their relation to systemic diseases N Y., Joseph Purcell Research Memorial, 1930 2 v

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Nelson new loose-leaf medicine. 1 Infectious diseases N Y, T Nelson & Sons, [1930-1939]

- Ormerod, F C Tuberculosis of the upper respiratory tract London, J Bale, 1939 215 p
- Pelouze, P S Gonorrhoea in the male and female, 3 ed, Phil, W B Saunders Co., 1939, 489 p
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- Virus and rickettsial diseases A symposium held at Harvard school of public health 1939 Cambridge, Harvard Univ Press, 1940 907 p
- Willensky, A O Osteomyelitis its pathogenesis, symptomatology and treatment. N Y, Macmillan Co, 1934, 454 p
- Wolbach, S B, Todd, J L & Palfrey, F W The etiology and pathology of typhus Cambridge Harvard Univ Press, 1922, 222 p 34 pl
- William J Matheson Commission Epidemic encephalitis Etiology, epidemiology, treatment. Third report N Y, Columbia Univ Press, 1939, 493 p
- Zinsser, Hans, Enders, J F & Fothergill, L D Immunity principles and application in medicine and public health 5 ed of, "Resistance to infectious diseases" N Y, Macmillan Co, 1939, 801 p

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- Journal of Hygiene. Cambridge, England
- Journal of Infectious Diseases Chicago
- Revista de patologia infecciosa Buenos Aires
- Zeitschrift für Hygiene und Infektionskrankheiten Berlin

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETING

MAY 15—*The Harvey Society in affiliation with The New York Academy of Medicine* The eighth Harvey lecture, "Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci," Rebecca C Lancefield, Associate, The Rockefeller Institute for Medical Research ¶ Report on election of Academy Fellows

SECTION MEETINGS

MAY 2—*Surgery* Executive session—a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee—for Chairman, Frank B Berry, for Secretary, Frank J McGowan, for member of Advisory Committee, Grant P Pennoyer ¶ Presentation of cases—a] Human bites of the hand, Roland L Maier, Discussion, Norman L Higinbotham, b] Cases illustrating first paper of the evening, Lester Blum ¶ Papers of the evening—a] The use of partial myotomy in flexor tenorrhaphy, Lester Blum, Discussion, John H Garlock, b] Technique for drainage of suppurative tenosynovitis of fingers and their extension into the flexor base of forearm, Hugh Auchincloss, Discussion, Philip C Potter, c] Puncture wounds of the hand, Condict W Cutler, Jr, Discussion, Kenneth M Lewis ¶ General discussion

MAY 6—*Dermatology and Syphilology* Executive session—a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee—for Chairman, Louis Tulipan, for Secretary, Timothy J Riordan, for member of Advisory Committee, George C Andrews ¶ Presentation of cases—a] Beth Israel Hospital, b] Brooklyn Jewish Hospital, c] Cornell Medical College Clinic, d] Miscellaneous cases ¶ Discussion of cases

MAY 6—*Combined Meeting Neurology and Psychiatry and the New York Neurological Society* Executive session—a] Reading of the minutes, b] Election of Academy Section Officers and member of Advisory Committee—for Chairman, George H Hyslop, for Vice-Chairman, Harold G Wolff, for Secretary, Charles Davison, for member of Advisory Committee, Samuel Brock ¶ Presentation of cases—a] Salvarsan encephalitis with recovery, E D Friedman, Ernest Newman (by invitation), Discussion, Bernhard Dattner (by invitation) ¶ Papers of the evening—a] Brain abscess of uncommon origin, relation to osteomyelitis of the skull (clinico-pathological study), Victor W Eisenstein, Pittsburgh (by invitation), E D Friedman, Charles Davison, Discussion, Joseph J King, Edmund P Fowler, Joseph H Globus, b] Electrical injuries of the central nervous system, Leo Alexander, Boston (by invitation), Discussion, Lewis D Stevenson, Armando Ferraro

MAY 8—*Pediatrics* Case demonstrations from 7 30 to 8 00 o'clock ¶ Executive session—a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee—for Chairman, Alfred G Langemann, for Secretary, Edith M Lincoln, for member of Advisory Committee, Leslie O Ashton ¶ Presentation of single case reports—a] Willard Parker Hospital—A case simulating poliomyelitis, Agnes G Wilson (by invitation), b] Lincoln Hospital—Cerebral embolus in a case of rheumatic fever, Edward Press (by invitation), c] New York Hospital—A case of bleeding due to prothrombin deficiency during gastrointestinal intoxication, Martin J Glynn (by invitation) d] Bronx Hospital—Meconium ileus, Bernard S Denzer, e] New York Post Graduate Hospital—Case for diagnosis—possibly atypical leukemia, Martin Green (by invitation), f] Lenox Hill

Hospital—Meconium ileus, Irwin P Sobel, g] Long Island College Hospital—Multiple hemangiomata with special reference to hemangioma of the spinal cord, Stanley S Lamm (by invitation), h] Beekman Hospital—Cooley's anemia in youth of 18 years observed since early childhood familial aspects, Carl H Smith, i] Babies Hospital—Congenital diaphragmatic hernia—operation at twelfth week of age, William G Heeks (by invitation), j] Beth Israel Hospital—Duodenal ulcer with massive hemorrhage in a child, Albert B Newman (by invitation), k] Roosevelt Hospital—A case of auricular paroxysmal tachycardia in an infant one-month old, Edmund N Jovner III (by invitation), l] Mount Sinai Hospital—Epidural granuloma associated with osteomyelitis of the spine, Ralph E Moloshok (by invitation), m] Polyclinic Hospital—Cardiospasm in the newborn relieved by atropine, Sidney V Haas, n] St Luke's Hospital—Duplication of the ileum with bleeding ulcers, Charles W Neuhardt (by invitation)

MAX 14—*Historical and Cultural Medicine* Executive session—a] Reading of the minutes, b] Election of Section Officers and member of Advisory Committee—for Chairman, Claude E Heaton, for Secretary, Herman Goodman, for member of Advisory Committee, Ramsay Spillman ¶ Papers of the evening—a] History of fever therapy, William Bierman, Discussion, Bernard Dattner, b] The history of electrodiagnosis, Sidney Licht (by invitation), Discussion, Saul L Heller ¶ Discussion

MAX 16—*Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Election of Section Officers and one member of Advisory Committee—for Chairman, Joseph Buchman, for Secretary, Donald E McKenna, for member of Advisory Committee, Lewis Clark Wagner ¶ Papers of the evening—a] The treatment of congenital club foot, methods and results (motion pictures and lantern slides), Malcolm B Coutts

(by invitation), b] Caisson disease of the bones, Carmelo C Vitale (by invitation), c] X-ray findings in alkaptonuria and ochronotic arthritis, Maurice M Pomeranz, Lewis J Friedman, Isidore S Lunick (by invitation) ¶ General discussion

MAX 19—*Ophthalmology* Executive session—a] Reading of the minutes, b] Election of Section Officers and one member of Advisory Committee—for Chairman, Kaufman Schlivek, for Secretary, Brittain F Payne, for member of Advisory Committee, Algernon B Reese ¶ Presentation of cases—a] Uveoparotid fever, Plinio H Montalvan (by invitation), b] Result after twenty-five years in a case of fat implantation into Tenon's capsule, Julius Wolff, c] Crystalline deposits in the cornea, A Russell Sherman, Newark (by invitation), d] Three generations of corneal dystrophy, Sigmund Schutz (by invitation), e] Alkaptonuria with ochronosis of sclera (three cases), James W Smith, f] Arachnodactylia with successful cataract extraction, William McLean ¶ Motion pictures—a] Applied anatomy of the lens, Henry Miniski, b] Intracapsular extraction of subluxated lens (1) with loop (2) with suction, Ramon Castroviejo, c] Repair of depressed fracture of lower orbital margin with rib cartilage, Wendell L Hughes, Hempstead, d] Relief of lid retraction in thyroid disease, Daniel B Kirby ¶ General discussion

MAX 20—*Combined Meeting of the Section of Medicine and the New York Heart Association* Executive session—a] Reading of the minutes, b] Election of Section Officers and one member of Advisory Committee—for Chairman, Asa L Lincoln, for Secretary, Irving S Wright, for member of Advisory Committee, Oswald R Jones ¶ Papers of the evening—a] The neurocirculatory adjustments during flying—physiological aspects, Ross A McFarland, Ph.D., Harvard University, Discussion Dickinson W Richards, Jr, b] Clinical as-

pects, Ashton Graybiel, Massachusetts General Hospital (by invitation), Discussion, Louis H. Bauer ¶ General discussion

Genito-Urinary Surgery — The following were elected at the April Meeting of the Section: Chairman, Frank Coleman Hamm, Secretary, Frank P. Twinem, member of Advisory Committee, Simon A. Beisler. No meeting of the Section was held in May due to the meeting of the American Urological Association at Colorado Springs, May 19-22.

MAY 21—*Otolaryngology Executive session*—a) Reading of the minutes, b) Election of Section Officers and one member of Advisory Committee—for Chairman, Page Northington, for Secretary, Ward C. Denison, for member of Advisory Committee, James W. Babcock. ¶ Case reports—a) Pneumococcus, type 3, meningitis of sphenoiditic origin, operation, recovery, b) Hemolytic streptococcus bacteremia of sphenoiditic origin, operation, recovery, Irving B. Goldman, c) A case of complete, bilateral, congenital occlusion of the nares, Arthur J. Huey, Walter P. Griffey (by invitation), d) Chemotherapy, internal and local, in a case of subperiosteal mastoiditis with sinus involvement, Staphylococcus albus, operation, recovery, Earl E. Baker (by invitation) ¶ Papers of the evening—a) The effect of running cold water in the ears of guinea pigs, Paul Miller Osman (by invitation), b) The effect of androgen therapy on the voice and larynx of women, Joseph L. Goldman, Discussion, Udall J. Salmon (by invitation), c) The Sonovox, James S. Greene

MAY 27—*Obstetrics and Gynecology Executive session*—a) Reading of the minutes, b) Election of Section Officers and one member of Advisory Committee—for Chairman, Harry Aranow, for Secretary, William T. Kennedy, for member of Advisory Committee, Frank R. Smith. ¶ Papers of the evening: Program by Woman's Hospital—a) Premature separation of the placenta, Ralph L. Barrett, b) Essential mechanical factors for urinary continence in females, William T. Kennedy, c) Roentgen therapy for acute postpartum mastitis, Harriet McIntosh (by invitation), d) Erythroblastosis, Lyman Burnham (by invitation), e) Results of subcutaneous implantation of crystalline estrogen and progesterone, Daniel R. Mishell (by invitation), Leon R. Motiloff (by invitation)

AFFILIATED SOCIETIES

MAY 19—*New York Roentgen Society in affiliation with The New York Academy of Medicine* Papers of the evening—a) The Cyclotron and its possible application to therapy, John R. Dunning (by invitation), b) The use of artificially radioactive substances in cancer therapy, John M. Kenney (by invitation) ¶ Discussion—Edith H. Quimby, Cornelius P. Rhoads (by invitation), Lloyd F. Craver (by invitation) ¶ Executive session

MAY 22—*New York Pathological Society in affiliation with The New York Academy of Medicine* Paper of the evening—The cancer problem now a roving commentary, Peyton Rous, Rockefeller Institute for Medical Research

DEATHS OF FELLOWS

FEINBERG, ISRAEL LOUIS 111 East 61 Street, New York City, born in New York City, July 3, 1870, died in New York City, April 12, 1941, graduated in medicine from the University of the City of New York in 1893, elected a Fellow of the Academy, May 5, 1904

Dr Feinberg served as one of the four coroners of the City of New York from 1910 to 1918 and was president of the Board of Coroners for that period. In 1914 he advocated abolition of the coroner system and urged the substitution of the medical examiner system which is now in use

McCoy, JOHN CHARLES 292 Broadway, Paterson, New Jersey, born in Paterson, March 19, 1867, died in New York City, April 17, 1941, graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1891, elected a Resident Fellow of the Academy November 16, 1899 and became an Associate Fellow in January 1904

Dr McCoy was consulting surgeon to the Paterson General Hospital, the Paterson Eye and Ear Infirmary, the Dover General Hospital, Holy Name Hospital at Teaneck, and the Good Samaritan Hospital at Suffern, New York. He had practiced surgery for fifty years except for the period when he served in France during the war as a Major and Lieutenant-Colonel. For his work with the AEF the Distinguished Service Medal was awarded him

Dr McCoy was a Fellow of the American College of Surgeons and one of its founders, a Fellow of the American Medical Association, a diplomate of the American Board of Surgery and a member of its founders' group, and a member of the County and State Medical Societies of New Jersey. At his death, he was Chairman of the Passaic County Medical Preparedness Committee

NICOLL, MATTHIAS, JR. Rye, New York, born in New York City, February 12, 1868, died in Rye, May 13, 1941, received the degree of B.A. from Williams College in 1889, and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1892, elected a Fellow of the Academy December 4, 1902

Dr Nicoll was New York State Commissioner of Health from 1923 to 1930 and Westchester County Health Commissioner from 1930 until his retirement in 1938. From 1908 to 1914, he was assistant director of the New York City Department of Health and chief of its division of diagnosis. In 1915 he entered the State Public Health Service as director of public health education and secretary of the State Department of Health, and from 1917 to 1923 he served as deputy State Commissioner of Health. Dr Nicoll was connected with the Willard Parker Hospital for thirteen years in his early professional career. Later, he again became associated with this hospital as consulting physician, where he worked with the late Dr William H. Park, former Director of the Bureau of Laboratories of New York City Department of Health. Together, in 1914, they gave the first demonstration of the value of intraspinal use of tetanus antitoxin in the treatment of lockjaw. He was at one time clinical professor in infectious diseases at University and Bellevue Hospital Medical School and was associated with the old Chamber Street Hospital, the Seton Hospital and the New York Foundling Hospital

Dr Nicoll was the author of numerous articles on pediatrics, infectious diseases, laboratory research and public health administration. He was a former president of the State and Provincial Health Authorities of North America, a Fellow of the American Public Health Association, a Fellow of the American Medical Association and its Chairman of the Section on Preventive and Industrial Medicine and Public Health 1925-1926, and a member of the State and County Medical Societies

1941 GRADUATE FORTNIGHT

OCTOBER 13 TO 24

"CARDIOVASCULAR DISEASES INCLUDING
HYPERTENSION"*The Program Includes*MORNING PANEL DISCUSSIONS, AFTERNOON CLINICS, EVENING
LECTURES, SCIENTIFIC EXHIBITS AND DEMONSTRATIONS

EVENING LECTURES

The subjects and speakers at the evening lectures are

<i>Basic hemodynamic principles essential to interpretation of cardiovascular disorders</i>	Carl Wiggers
<i>Heart failure</i>	Paul D. White
<i>Coronary insufficiency Observations on diagnosis and treatment</i>	Robert L. Levy
<i>Pathology of arteriosclerosis, with special reference to coronary arteries</i>	Timothy Leary
<i>Arteriosclerosis Social significance and recent advances in treatment</i>	George M. Piersol
<i>Advances in our knowledge of endocarditis with special reference to the therapy of subacute bacterial endocarditis</i>	Emanuel Libman
<i>Neurocirculatory asthenia and related problems in military medicine</i>	B. S. Oppenheimer
<i>Syphilis of the cardiovascular system</i>	Edwin P. Maynard, Jr.
<i>Arrhythmias including paroxysmal tachycardia and their treatment</i>	Isaac Starr
<i>The value and limitations of the electrocardiogram in medical practice</i>	H. M. Marvin
<i>Evaluation of drugs used in the treatment of cardiovascular diseases</i>	Arthur C. DeGraff
<i>Surgery of the heart and large vessels</i>	Edward D. Churchill
<i>Surgical treatment of peripheral embolism and peripheral aneurism</i>	Gerald H. Pratt
<i>Thrombophlebitis</i>	Irving S. Wright
<i>Heparin</i>	D. W. Gordon Murray
<i>Raynaud's disease</i>	James C. White
<i>Thromboangitis obliterans</i>	Edgar V. Allen
<i>Experimental studies related to shock</i>	Magnus I. Gregersen
<i>Influence of extrinsic factors on the coronary flow and the clinical course of heart disease</i>	N. C. Gilbert
<i>Treatment of heart disease in childhood</i>	T. Duckett Jones
<i>Management of heart disease in pregnancy</i>	Harold E. B. Pardee
<i>Mechanism and treatment of pulmonary edema</i>	Soma Weiss
<i>Natural history of rheumatic cardiac disease</i>	Alfred E. Cohn
<i>Mechanism of essential hypertension</i>	Harry Goldblatt
<i>Effects of renal extracts on hypertension</i>	Winslow R. Harrison

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



OCTOBER 1941

NEWER SURGERY OF THE HEART AND
LARGE VESSELS MEDICAL ASPECTS*

H M MARVIN

Associate Clinical Professor of Medicine Yale University School of Medicine

IT was with deep gratification that I received and accepted the invitation to participate in the exercises of this evening, and I wish first of all to express my lively appreciation of the honor and the privilege of appearing once more in this hall as one of your speakers. It is surely unnecessary to tell a New York audience that my pleasure is all the greater because of the distinguished company in which I appear. I strongly suspect that my presence this evening is due to the fear, in the minds of your Committee, that if Dr. Andrus† were allowed to speak without opposition, as it were, his eloquence and enthusiasm might unintentionally lead many of you to magnify the advantages and minimize the disadvantages of surgery. I assume that mine was to be the voice of conservatism, and my function was to warn you urgently against the wiles and blandishments of our surgical brethren!

But if there was some such thought as this in the minds of those who arranged the program, circumstances have conspired to prevent its fulfillment. Through a series of misfortunes, of which illness was

* Presented at the Stated Meeting of The New York Academy of Medicine, February 6, 1941.

† William De Witt Andrus, Associate Professor of Surgery, Cornell University Medical College.

the chief one, Andrus and I were prevented from meeting, or even writing, to consider our respective parts in the program until about two weeks ago. It was immediately apparent to us, as I hope it will be later to you also, that it would be unprofitable for us to enter upon a joint discussion of the same surgical measures, as the printed announcements of the meeting seemed to promise. For in the first place there were so many operations deserving of mention that time would not permit both of us to comment on them, and in the second place we found that with respect to certain of the newer surgical procedures neither of us had any personal experience. This meant that we would have based our comments on the same published reports, and we would inevitably have said so nearly the same things that the result would have been painful both to the audience and the speakers. We therefore decided to divide the various procedures between us largely on the basis of personal experience or familiarity with them. And one unexpected result of this division of the topics is that I am to discuss with you chiefly those operations upon or in immediate relation to the heart, while Dr. Andrus will concentrate mainly upon surgery of the larger blood vessels, a field of great and increasing importance.

With this brief word of explanation, I should like to plunge at once into a consideration of two recent surgical measures designed to increase the blood supply of the heart.

The first of these is intimately associated with the name of Claude Beck of Cleveland. It has long been recognized that great diminution of the blood flow through the coronary arteries, resulting from sclerosis and narrowing of these vessels, is responsible for the majority of disability and deaths that are properly charged against heart disease. It is clear therefore that any measure which would augment the blood supply of a heart that is failing because of inadequate nutrition would be of the greatest possible value. After years of experimental work upon dogs, Beck was convinced that this purpose could be accomplished by attaching other tissues directly to the surface of the heart. In animals he employed pericardium, pericardial fat, omentum, and muscle, in man, a portion of the pectoral muscle only. He believed that blood vessels would grow from the healthy pectoral muscle into the anemic myocardium and would supply the heart with enough additional blood to improve its function. He performed the first such operation upon a human being in February 1935, and the last one apparently

about three years later

From the last published report of Beck in November 1937 a few facts may be briefly summarized. At that time twenty-five patients with advanced anginal heart failure had been subjected to the operation, nine of these had died and sixteen were living. Eight of the nine deaths occurred within a week after operation. The operative mortality was 50 per cent in the first twelve patients, but only 15 per cent in the following thirteen. Of the sixteen surviving patients, thirteen had been followed for five or more months after operation, three were thought to have shown great improvement, nine moderate improvement, and one slight improvement. The statement is made that "there were no patients who were not improved by the operation." At this time Beck recognized and frankly stated that the beneficial effects of the operation might be explained by any of several possibilities. One was an actual increase in the blood supply of the heart due to new vessels from the muscle graft, a second was a redistribution of blood in the coronary arterial system caused by opening up of intercoronary communications by trauma to the epicardial surface of the heart, and a third was the interruption of nerve pathways from the heart, which might prevent pain impulses from reaching the central nervous system.

Now on the basis of this report, one must admit that there was considerable ground for encouragement. An operative mortality of 15 per cent is certainly not excessive when one considers the serious condition of these patients before operation, and it is probable that further experience would have reduced this to a still lower figure. Of the thirteen patients observed for five or more months, twelve, or 92 per cent, are said to have shown moderate or great improvement. Why then did Beck cease performing the operation when the future appeared so promising? I am not certain that I can state all the reasons, but some of them seem to be fairly clear.

In the first place, I think there was growing uncertainty in the mind of Beck and his medical colleague Feil as to whether the muscle grafts were in fact providing the myocardium with a new supply of blood, or whether the early improvement might not be due to some other cause. Autopsies upon experimental animals had demonstrated the existence of vessels passing between the graft and the myocardium, but these were few in number and for the most part microscopic in size,

there was serious question as to whether these minute channels could convey enough blood to be of any real value. Furthermore, the mere demonstration that such vessels existed did not prove that the blood flow was from the graft into the myocardium, it was equally conceivable that it was in the reverse direction. Then it was not possible wholly to ignore the criticisms of experienced and thoughtful surgeons to the effect that the method of performing the operation materially lessened its chances of success, because the pectoral muscle, having been deprived of its nerve supply and having been placed at complete rest, must inevitably atrophy and therefore suffer a diminution in its own blood supply. Moreover, there was the demonstration by Burchell that much of the experimental work upon which the human operation was based contained a serious fallacy and did not justify the conclusions that had been drawn from it. I shall discuss this work of Burchell more fully in a moment, since it applies equally to the next operation. And finally, as Beck himself has stated, he was convinced that the value of the procedure must be determined ultimately by one thing only, namely, its demonstrable effects upon human cases, rather than by animal experiments or theoretical considerations. Having performed the operation upon some thirty patients, he decided that this was a group large enough to warrant at least tentative conclusions if the survivors could be carefully observed for some years or until the time of death.

Before stating briefly my own estimate of the operation, I should like to discuss another that is quite similar and designed for the same purpose. It consists of the attachment of a portion of the omentum, instead of the pectoral muscle, to the heart. This operation, known as cardio-omentopexy, was apparently first performed by Laurence O'Shaughnessy of London, who was tragically killed during the war in Flanders last June. Briefly, it consists of opening the pericardium and placing upon the epicardial surface of the heart a suitable portion of omentum brought from the abdomen through an opening in the diaphragm. Apparently O'Shaughnessy started his experimental work upon dogs before Beck had published any of his comparable observations, and the work of the two men has many striking similarities. They were both led to the conclusion that the heart could be abundantly supplied with blood from an outside source. In selecting the omentum as the new source of blood, O'Shaughnessy was influenced by the fact that one of the known functions of this tissue is to supply blood to other organs

that need it, and he stated that it was in fact the only tissue that has this function. In some instances the arteries that have grown from the omentum into other organs have been shown to increase greatly in size, whereas the vessels of the pectoral muscle graft, as already indicated, must be expected to grow smaller.

In the report by O'Shaughnessy and his colleagues in January 1938, it is stated that of the fifteen patients with anginal heart failure subjected to this operation, five had died, one on the operating table, and the remaining four, two to three months after operation. Of the ten who survived, eight became entirely free of anginal pain, and seven of these had returned to active work.

The sad events of the past seventeen months in Europe, and especially the tragic death of O'Shaughnessy, prevent our asking why the operation has not been continued in England, but one may ask why it has not been performed in this country. I have been unable to find a report of such an operation upon a human patient. Before attempting to answer this question I must ask you to go back with me and consider for a moment the experimental evidence upon which Beck and O'Shaughnessy relied. In general it was quite similar, and consisted essentially of the demonstration that it was possible to reduce the coronary blood flow greatly in dogs by constriction or ligation of coronary branches, and yet have the animal survive, provided a collateral circulation was previously established by the creation of external adhesions. Beck and Tichy, in their most successful experiment, estimated that approximately 85 per cent of the total cross sectional area of the main coronary arteries was occluded, yet the animal lived and was normally active. Complete occlusion of single main arteries or partial occlusion of several main stems was effected with survival of the animals, and this result was ascribed to the establishment of a collateral vascular bed by previous operations. O'Shaughnessy laid emphasis especially upon the ability of dogs to perform strenuous exercise some months after ligation of a main coronary artery, provided cardio-omentopexy had also been performed. The demonstration that greyhounds could race normally after such operations was interpreted as indicating that the omental graft had effectively counterbalanced the loss of a major coronary artery. It is true that both observers also secured some evidence of growth of vessels between the graft and the heart, but in most instances this seemed unconvincing or of such lim-

ited extent as to be unimportant. In general the evidence was indirect, and was interpreted, without adequate control, as indicating that the grafts did in fact supply the heart with a considerable quantity of blood.

And now I come to the observations of Burchell, to which I alluded a moment ago. He reexamined the entire question from the beginning and found a good deal of discrepancy in the reports of different observers upon the immediate and ultimate results of ligation of coronary arteries in the healthy dog, but it is of great interest, and quite relevant to the point now under consideration, that a number of operators prior to Beck and O'Shaughnessy had been able to ligate main arteries with a very low or quite moderate mortality rate. Burchell performed a series of ingenious experiments which resulted in marked constriction of coronary arteries or gradual complete closure of main arteries, in addition to sudden complete closure by ligation. He found that constricting collars with an internal diameter of 1.5 to 2.5 mm. could be placed on all three main coronaries in two operations about two weeks apart, and the animals subsequently showed no disability and could exercise on a sloping treadmill as well as normal animals. When he used a method that resulted in gradual complete occlusion of the vessel, he found that all three main arteries could be closed in successive stages without the production of infarction and without any impairment of the normal cardiac function. He also showed that if dogs survived the immediate effects of ligation of main coronary arteries, there was little or no evidence of cardiac disability after the healing of the infarct. Most surprising of all, he observed that in some instances dogs could survive acute ligation of all three main coronary arteries in successive operations if these were not tied too close to the point of origin, and one such dog seemed to be capable of normal physical activity subsequently. It was possible to prove that in such instances the hearts were nourished through the main coronary stems. You will understand, of course, that all these experiments were performed upon dogs that had not been subjected to any of the procedures employed by Beck and O'Shaughnessy, there was no question of a collateral circulation established by means of previous operation.

Having shown that all the results mentioned by Beck and O'Shaughnessy, as well as others far more spectacular, could be obtained in normal dogs without the use of grafts or pericardial adhesions, Burchell next examined the efficacy of tissue grafts as carriers of blood.

into the myocardium. He attached grafts of pectoral muscle or of omentum to the heart in the manner described by his predecessors, and was unable to demonstrate that they exerted any beneficial effect in preventing infarction of the ventricle after ligation of the anterior descending coronary artery. In most instances the thin layer of scar tissues between the graft and the myocardium contained blood vessels that could be seen only with the aid of a microscope. When the tissues were injected with india ink, this thin intervening layer usually appeared clear and avascular, even when the graft and the myocardium were heavily loaded with ink. It was observed that omental grafts formed adhesions to the heart that were very easily separated, and if no injury had been done to the epicardium, adhesions were often completely absent. There was no evidence of increase in vascularization with progressive coronary occlusion, as O'Shaughnessy had assumed there might be, and in only one instance was it possible to demonstrate barium in the coronary vessels after this substance was injected into the omental graft.

He was unable to demonstrate that the vessels seen in the adhesions carried any significant volume of blood. By means of heart-lung preparations he calculated in two animals that the total volume was $\frac{1}{2}$ to 2 cc per minute, while in two others where occlusion of all three arteries had been effected, no flow through the adhesions could be demonstrated, although the grafts had been in place from 9 to 20 months.

And lastly, Burchell performed the crucial experiment that both Beck and O'Shaughnessy omitted. In three dogs muscle grafts and in three, omental grafts were placed upon the heart, and occlusion of the three main coronary arteries was produced. The animals survived and were normally active. You will recall that it was evidence of this type, although far less convincing and extensive, which led Beck and O'Shaughnessy to conclude that in these circumstances the heart was deriving its blood supply from the graft. But they did not perform the logical experiment that would have proved decisive. Burchell did. He cut the grafts from the hearts in all six animals. You will probably not be surprised when I tell you that the animals were not inconvenienced by removal of the graft, that their ability to work on the treadmill was not impaired, and that there were no electrocardiographic changes to indicate a diminution of blood flow to the myocardium.

I think one must conclude that unless these observations of Burchell

are shown to be inaccurate, which seems to me unlikely, they remove every particle of *experimental* justification for the muscle graft and omental graft operations. But this does not necessarily prove that the operations are devoid of value in human cases, and we must consider briefly what results have been secured so far as this can be determined from available reports. You will recall that in Beck's last published report the statement was made that there was no patient who was not improved by the operation. But as I heard Beck present this material in New Haven, with details and case reports, it seemed to me that only three had shown sufficient improvement to justify a procedure that was attended by an operative mortality of at least 15 per cent. At the time these three had apparently shown considerable improvement, but in the light of our present knowledge the benefit cannot be ascribed without considerable hesitation to an increase in myocardial blood flow due to the graft, and may well have been due to interruption of nerve pathways or to a redistribution of blood in the coronary arterial system. Within the past few weeks Beck has stated frankly that he does not know if the operation has value. Of the patients who survived, only three have subsequently died after periods long enough to make observations upon them of value. Autopsy in one case apparently confirmed the clinical impression that little if any benefit had been derived from the procedure, there was no anatomical evidence that the graft had provided the heart with additional blood. A second patient had apparently been helped by operation, and autopsy showed about a dozen very fine, hair-like vessels running between the graft and the heart muscle. When barium was injected into the coronary vessels, it emerged from the vessels of the graft, but the cleared specimen showed only very minute channels. The clinical result in this case is said to have been far better than would have been expected on the basis of the anatomical findings at autopsy. Beck suggests that for the present the group be regarded as one subjected to a purely experimental procedure, rather than to one of known therapeutic value. If there seems to be some lack of harmony between these later conservative statements and the earlier estimates of therapeutic benefit, it is at least greatly to his credit that he has been willing to alter his views in accord with accumulating experience.

This is perhaps as far as we can go in stating the known facts, for there have been no later reports upon the patients subjected to omentopexy. What then shall we say as to the value of these operations and

their place in future cardiac therapy? Recognizing that our information is still incomplete, it nevertheless seems to me most unlikely that either of them will ever be resumed. I think it is improbable that the improvement in the surviving patients was due to any significant increase in the blood supply of the heart, and if this purpose was not in fact achieved, the operation loses all justification. If some improvement occurred as an indirect result of the procedure, further observations are necessary to determine the mechanism of this and to ascertain if equal or greater improvement cannot be secured from a simpler operation attended by little or no mortality. We may surely wait for the final report upon the patients still living before pronouncing a final verdict, but I do not believe the available information warrants great optimism. The evidence that I have mentioned at some length seems to me clearly opposed to the belief that a valuable therapeutic procedure has been discovered.

I turn now for a few moments to a more recent operation, namely, ligation of the patent ductus arteriosus. As most of you know, the ductus is a vessel of variable size which runs from the aorta to the pulmonary artery, is a vital part of the circulation in the fetus but ceases to serve any useful function after birth and normally closes and atrophies within the first few months of life. When it remains open, it constitutes in essence an arteriovenous fistula through which relatively enormous quantities of blood pass from the aorta into the pulmonary artery because of the much higher pressure in the former vessel, and this leak is continuous through systole and diastole. The blood from the aorta, having been shunted into the pulmonary artery, flows into the lungs, then back to the left ventricle from which it was pumped only an instant before. If the duct is a fairly large one, only a small portion of the left ventricular output is available for the peripheral circulation, which is consequently partially starved.

These mechanical aspects readily explain several of the more important clinical findings associated with the condition. The pulmonary artery becomes moderately or greatly dilated, and there is considerable engorgement of the pulmonary vascular bed because of the tremendous increase in the volume of blood now flowing to the lungs. If the leak from the aorta is of considerable magnitude, it results in the classical signs of aortic regurgitation, namely, a low diastolic pressure, a wide pulse pressure, Duroziez' sign, and usually enlargement of the left ventricle. Some idea of the amount of increased work thrown upon the left

ventricle in cases of large shunts may be obtained from the studies of Ep-pinger, Gross and Burwell upon some of the patients subjected to operation. They found, for example, that in one patient the peripheral blood flow per minute was approximately 6 liters, while the pulmonary blood flow was more than 25 liters¹. The volume of blood flowing through the duct was 19.5 liters, or 77 per cent of all the blood entering the pulmonary circulation¹. In general, they state that from 45 to 75 per cent of the blood leaving the left ventricle passes through the ductus into the lungs, then immediately back into the left ventricle, without having accomplished its normal function of delivering oxygen to the body's tissues. It is not surprising, in view of these figures, to learn that a number of patients with patent ductus are undernourished, and it is easy to understand why many of them die of heart failure induced by the enormous strain thrown upon the left ventricle.

Please do not misunderstand me as implying that all patients who have a patent ductus must inevitably suffer from malnutrition, 'cardiac enlargement, or heart failure. It is probable that these are invariable manifestations of a large shunt of blood from the aorta to the pulmonary artery, but there would appear to be at least a moderate number of patients who live for many years in perfect comfort with a small open ductus which imposes but little additional work upon the left ventricle. Even in this relatively fortunate group, however, there is a serious and ever-present menace to health—the danger of subacute bacterial endocarditis, which is known to occur in a certain percentage of people with this congenital anomaly.

The possible harmful effects of patency of the ductus, then, consist of malnutrition and underdevelopment of the child, the occurrence of congestive heart failure, and the development of subacute bacterial endocarditis or endarteritis. In the present state of our knowledge it is admittedly impossible to present any accurate figures as to the incidence of patency of the ductus in the general population, or as to the frequency of these complications. Statistics drawn from previous medical literature are worthless for at least two reasons—they represent a strictly selected group, and they include large numbers of infants. The inclusion of infants complicates the figures because the diagnosis of patent ductus is highly uncertain in the first months of life, because it is still unknown how long it may remain patent normally, and because bacterial endocarditis occurs rarely if at all in infancy. Figures as to the incidence of

patent ductus in large groups of autopsies are of doubtful value because there is general agreement that this anomaly is very readily overlooked in routine postmortem examinations, it often requires the most careful search to demonstrate its presence, and it seems probable that it occurs in a higher proportion of cases than has been thought in the past. I am in full agreement with those recent writers who have stated emphatically that no reliance should be placed upon conclusions drawn from such a group as that of the late Dr. Abbott, for the reasons just stated, I refer specifically to this group because it has been quoted in almost every paper written on this subject in the past two years.

Now inasmuch as the three dreaded complications of this condition are all due to the presence of an abnormal channel, it has long been recognized that they might be prevented by the mechanical closure of this duct. The first attempt to ligate an open duct was made, unsuccessfully, in 1937, and it remained for Robert Gross of Boston to perform the first successful closure in a human being, in August 1938. Within a short time he had performed the operation successfully, and with great benefit, upon others, and it was not long before surgeons in other cities were following his example. I have made no attempt to compile a complete list of the operations performed up to the present time, but I can tell you that on January 13, when I had a very happy and profitable meeting with Gross, Burwell, and Eppinger in Boston, Gross had operated upon twelve uninfected cases and one complicated by subacute bacterial endocarditis. There had been only one postoperative death, and that was caused by a *Staphylococcus aureus* infection. Bullock, Jones, and Dolley of Los Angeles have reported thirteen cases, there was only one postoperative death in their group, and that also was due to *Staphylococcus aureus* infection. A letter received yesterday from Dr. Bullock informs me that their group now comprises sixteen cases, and there have been no other postoperative deaths. George Humphreys of this city has very kindly provided me with full details of four patients upon whom he has operated at the Babies Hospital, a fifth one operated upon by John Sullivan at Bellevue, and a sixth one (the only adult) subjected to operation by Dr. Blakemore at Presbyterian Hospital. Emile Holman of San Francisco writes me that he has operated upon only one patient with patency of the ductus, and Alfred Blalock of Nashville has ligated the duct in one patient with bacterial endocarditis and one without this complication. Arthur Touroff of New York has operated upon four

patients who were known to have bacterial endocarditis at the time of operation, and I shall have a word to say about these in a moment. There are probably many others operated upon but not yet reported, but these form a group sufficiently large to justify certain comments.

I think it is worthy of emphasis that the operative and postoperative mortality has been extremely low in the uninfected cases. The mortality in the small group in this city is still zero, while in the larger groups of Boston and Los Angeles there have been only two postoperative deaths, both of them from a type of infection that might have occurred after any surgical procedure, and therefore not to be regarded as a specific argument against closure of the ductus.

Those who advocate the operation do so for three reasons. They believe that it will correct malnutrition when this is present, that it will prevent heart failure, and that it *may* prevent the development of bacterial endocarditis. In the cases thus far reported there has apparently been remarkable improvement after operation with respect to nutrition and also with respect to the signs of cardiac enlargement and of heart failure. I may add that theoretically there is every reason to believe that the operation stands upon unassailable ground with respect to these two indications. But when we consider the effect of the operation upon the possibility of subsequent bacterial endocarditis, we immediately enter the field of speculation. We have no proof as yet, and in the nature of the case cannot secure such proof for years, that successful closure of the duct will prevent the subsequent occurrence of a *Streptococcus viridans* infection in the wall of the aorta or the pulmonary artery where the duct formerly existed. Theoretically, there is reason for believing that unless the operation is done in early childhood, the changes in the pulmonary artery may have progressed so far that this complication may occur even if the duct is closed surgically. To say that no operated case has thus far developed bacterial endarteritis is irrelevant, for it is known that this infection may develop late in life, and we shall have to wait some years before we can speak with confidence of this particular aspect.

But in this connection a special word should be said about the group operated upon by Dr. Touroff of this city. He has courageously attempted to close the duct surgically in four patients who were known to have bacterial endarteritis already, the families and medical advisers of the patients elected this desperate measure because of the hopeless outlook. His first patient has apparently been completely cured of the infec-

tion by ligation and division of the duct, a second one was not helped by closure of the duct, and the other two died of operative complications, which are almost insuperable in the presence of an infection of long standing I think Touroff deserves our congratulations upon his courage and skill, in extending them, I wish also to express my warm thanks for his kindness in giving me so generously of his time and thoughts when we discussed his cases several weeks ago I should like to add that in my opinion the almost absolute certainty that death will occur from the infection in these patients is sufficient to justify the admittedly hazardous operation The fact that it has been successful in one of the two surviving patients in Touroff's group may prove to be highly significant

At the present moment, then, I think we may safely say that surgical ligation of the duct is indicated in those patients who have enlargement of the heart, and those with imminent or actual heart failure If there is distinct enlargement of the ventricle and this increases under observation, it is highly probable that heart failure will soon appear Malnutrition by itself is almost certainly not an indication, since this is associated with a large shunt, which would lead to ventricular enlargement

One word of caution seems to me not only permissible, but also essential It is perhaps natural and inevitable that a wave of enthusiasm should sweep the country when a new and promising therapeutic procedure is introduced Sometimes the enthusiasm is so great as to abolish critical judgment temporarily, and the procedure is applied without proper discrimination to many patients for whom it is unnecessary or actually contraindicated Already we are being asked to arrange for this operation upon patients who have signs of patent ductus but no evidence of disability, cardiac enlargement, or heart failure If we knew that such patients would almost certainly develop bacterial endarteritis without the operation and could be promised immunity after the operation, and if, furthermore, the operative mortality remains extremely low, then the procedure would be indicated But we do not know this as yet Shapiro of Minneapolis has observed nineteen patients with patent ductus, some of them as long as 17 years, and none has developed heart failure or bacterial endocarditis, Stroud of Philadelphia has observed ten such patients in the past 20 years, and none has developed either of these complications It is perfectly possible that a majority of these twenty-nine patients may yet die of heart failure or streptococcus infections, but we have no justification as yet for assuming this

I would not for one moment state or imply that Gross' achievement in perfecting this operation is anything less than his admirers have proclaimed it to be, but perhaps it is my duty to remind you that the great chorus of praise and adulation that has been raised in his honor has a strange resemblance—to my ears at least—to that raised in honor of certain other surgeons within the past fifteen years, whose marvellous contributions have now been forgotten and abandoned. It is my own belief that this operation stands upon a firmer foundation than any of these others, on the basis of our present rather slight knowledge, I believe it will occupy an important place in the treatment of a condition hitherto not accessible to therapy, but I think its ultimate place may be a smaller one, from a numerical standpoint, than certain others now appear to believe. The operation seems to me a noteworthy achievement, of great value in a rather limited group.

The three operations just discussed are so recent that, as I have indicated, it is impossible at this moment to express any final judgment upon their real value and their ultimate place in the therapy of heart disease. In the time that remains I should like to speak briefly of a group of operations which may be appraised with greater confidence because they are of less recent development. Of these there are four that seem deserving of comment.

The first is total thyroidectomy, an operation proposed a few years ago for the relief of anginal or congestive heart failure. Those who sponsored the procedure stated—and I express their statements in a very general way—that heart failure might be ascribed to a discrepancy between the demands of the body and the ability of the heart to meet those demands. If the usual therapeutic measures did not abolish this discrepancy by improving the heart's functional ability, they thought it possible that lowering the demands of the body, by decreasing the basal metabolic rate, might do so. The results of the operation in the early cases seemed quite promising, although many observers refused to accept it because of certain discordant results and because the physiological foundation for the procedure was by no means clear or convincing. I think one may say now in all fairness that the operation has been almost completely abandoned, even by those who introduced it and were most enthusiastic several years ago. Blumgart believes that it is of value in occasional patients whose heart failure is progressive despite all other therapeutic measures, and Geoffrey Bourne of England has reported

highly satisfactory results in a small group of anginal patients within the past few months I doubt if the reported results justify the scornful rejection with which it has met, but on the other hand I seriously doubt if it will ever come into general use, and I think its value is slight

A second operation performed upon structures outside the heart in the hope of relieving symptoms of heart failure consists of the injection of alcohol into the upper thoracic sympathetic ganglia. Many of you are aware that the nerve fibers which convey pain impulses from the heart into the central nervous system appear to converge in the upper four sympathetic ganglia, whence they are conveyed across the communicant rami into the posterior nerve roots and the spinal cord. All such impulses may therefore be interrupted if these nerve structures are sectioned or blocked by the injection of alcohol into them. The surgical resection of the posterior nerve roots is a difficult operation, attended by an excessive mortality rate, so injection of alcohol is preferable. If the alcohol is placed accurately in or immediately adjacent to the ganglia, the results are highly satisfactory, and anginal pain is completely or almost completely relieved in from 70 to 90 per cent of the patients. It is very seldom necessary to repeat the procedure because of regeneration of nerves, in some cases the relief has continued without change for a number of years. The operation is a relatively simple one, performed under local anesthesia, and there is practically no operative mortality, but unfortunately its success depends upon long experience and constant practice, so there are very few surgeons who are competent to perform it satisfactorily. This procedure is associated chiefly with the name of James White of Boston, whose series is much the largest in the country. His results have been little short of spectacular, when one considers that he has selected for operation only those patients who have advanced anginal failure and whose lives are almost insupportable despite the best possible medical treatment. I can testify that some of my patients upon whom White has performed this operation have been transformed from complete invalids into normally active individuals free from pain. The only serious objection to the procedure is the occurrence of alcoholic neuritis of the intercostal nerves in a majority of the patients. This may be quite distressing and often lasts for some weeks, but it eventually subsides, leaving normal cutaneous sensation. Despite this real disadvantage, it seems to me this is far the most useful of the surgical measures available for the treatment of those anginal patients who no longer re-

spond satisfactorily to medical therapy. In my opinion it is vastly superior to total thyroidectomy for this purpose.

Lastly I wish to speak very briefly of two operations relating to the pericardium. The first is that sometimes known as the Brauer operation, or by the unfortunate term "cardiolysis," and consists of the removal of portions of the ribs overlying the heart, usually of the 3d, 4th, 5th, and 6th ribs on the left. The operation was originally suggested because of the belief that if the two layers of the pericardium are adherent, and in addition the external layer is densely adherent to the ribs, sternum, and mediastinal structures, the work of the ventricles will be enormously increased because they must in these circumstances pull inward upon a dense, rigid cage at each contraction. Inasmuch as section of the adhesions was thought to be difficult and unsatisfactory, it was proposed to remove the bony attachment of these adhesions, and thus permit the heart to tug upon a soft yielding flap of muscle and skin, instead of bone. The underlying conception has been vigorously assailed in recent years by Beck, who insists that external adhesions of the type just described are not of importance, do not cause cardiac enlargement or heart failure, and are not an indication for operation. There are some, perhaps many, who agree with him, but I am not yet ready to number myself among them. Such experienced observers as Evarts Graham, Bigger, and Blacklock have indicated that in their opinion the operation may stand upon a firm basis, although perhaps in a smaller number of cases than was believed a few years ago, and a number of authentic cases have been reported in which dramatic relief of heart failure followed the resection of adhesions or the removal of ribs over the heart. I have myself witnessed such conspicuous improvement in a few patients that I am quite unwilling to subscribe to the view that the operation is valueless. It is quite possible, however, that in some cases the improvement may be due, not to a lessening of the heart's work, but rather to having afforded a large heart more adequate space in which to work. It is my belief that the operation is of great and proven value in a small group of cases.

And lastly I wish to refer to the operation known as pericardiectomy, performed for the relief of signs and symptoms known collectively as the Pick syndrome. These include, among the more important, high venous pressure, low arterial pressure, ascites, a heart that is normal in size or smaller than normal, and usually absence of signs of heart disease. This syndrome is now known to be due to constriction of the

heart by a dense pericardium, which may be extensively calcified or otherwise thickened. The heart is so densely held by this constricting envelope as to be unable to dilate and fill normally in diastole.

The surgical treatment is clearly indicated by this brief description, and consists of the removal of the pericardial scar in whole or in part. When this is successfully performed, the results are most gratifying. Inasmuch as the heart itself is seldom diseased, the removal of its mechanical handicap restores it to normal function, and there is usually a rapid disappearance of the signs and symptoms just mentioned. A large number of patients have been subjected to the operation, the major groups having been reported from the New York Hospital, from Boston, Cleveland, and Nashville. A few minutes ago, at the dinner preceding this meeting, Bernard Oppenheimer told me that he and his associates (Hitzig and Neuhof) have just reported a group of eight patients with this condition upon whom operation has been performed. Five of them showed marked improvement or complete recovery, the periods of observation extending from several months to eight years. Three died, two of them within a week of operation and the other many months later of carcinoma. I am sure Dr. Oppenheimer will not object to my mentioning these patients inasmuch as his report upon them is already in press. Of all the operations upon the heart or pericardium, this seems to me the most important in its results, and perhaps the greatest contribution that surgery has yet made to this field. I hope that Dr. Andrus will tell us of his own experiences with it.

One final word by way of summary and I shall be through. Of the operations mentioned, I believe that those designed to provide the heart with a new source of blood are probably valueless. Surgical ligation of the patent ductus arteriosus seems destined to be of immense importance in a group of patients that will probably always be numerically small. Total thyroidectomy may have a limited place, but in the absence of an elevated basal metabolic rate the indications for it are not very clear and the results are apt to be unsatisfactory. Alcohol injections into the thoracic sympathetic ganglia have been proven highly satisfactory by years of experience. The Brauer operation for adhesive mediastino-pericarditis seems to me of demonstrated value in a few cases, and I think the time has not come to discard it. And pericardiectomy for constrictive pericarditis may be confidently regarded as a major therapeutic procedure and a brilliant surgical contribution.

MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS OF THE CORONARY CIRCULATION

Harvey Lecture, April 18, 1940

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PROBLEMS for investigation which have their origin in the clinic frequently lead the investigator far afield in the course of his search for suitable methods for their solution. Interesting side trips into pathology, physiology or chemistry may result when he is forced to use the methods or seek the help of his colleagues in these subjects. And so it is with the work concerning which I have the honor to speak to you this evening. It had its origin in the clinic and has been carried on during the past ten years in the Department of Medicine of the Lakeside Hospital and Western Reserve University. In the various stages of the work I have had the privilege of having with me a number of younger collaborators, and we have sought and obtained aid frequently from our colleagues, particularly in physiology, chemistry, and pathology. The final result, therefore, may be said to be the product of all of these.

The coronary vascular tree, which supplies blood to the heart, is—with its various ramifications and anastomoses—one of the most complex vascular systems in the body. For this reason, it seems wise to begin with a description of the structure of the coronary circuit and its numerous component parts.

When Galen¹ first applied the name “coronary” to the larger arteries of the heart he was in doubt, apparently, as to whether there was one or two such vessels, and the confused conception which he held concerning their function is brought out by his suggestion that the arteries ended as nerves. It was not until the great publication of William Harvey² that the first clear statement of their function appeared. In his *De Motu Cordis*, Harvey states that the heart has a supply of blood for its own especial behoof, in its coronary veins and arteries—“hic locus autem cor est, cum solum ex omnibus partibus (non solum in vena &

arteria coronali privato usui) sed in cavitatibus suis tanquam in cisternis, & promptuario (auriculis scilicet & ventriculus) publico usui, sanguinem continet ”

The coronary vessels are shown in the anatomical drawings of Leonardo da Vinci, but it was not until the work of Richard Lower³ in 1671 that more accurate data concerning the arteries and veins of the heart began to appear. Lower was the first to describe anastomoses of the branches of the arteries, which he demonstrated by showing that liquid which he injected into one artery escaped from the other. Friedrich Ruysch⁴ in 1704 introduced the corrosion method of studying blood vessels and showed the distribution of their branches. Almost simultaneously Raymond Vieussens,⁵ in 1706 and 1715, published the results of his brilliant studies on the heart. His beautiful dissections of single branches of the coronary arteries revealed the distribution of the vessels in the various muscle layers. Of greater significance, however, was his discovery of a new group of blood channels in the heart wall. While opening human hearts at necropsy, he observed that the blood clots, so frequently seen in the heart chambers, had attached to them little tendrils which ran into small openings in the heart walls. Being convinced that these openings were connected with the coronary circuit, he injected saffron into the coronary arteries and observed its escape through the small openings into the auricles and ventricles. Two years later, in 1708, Adam Christian Thebesius⁶ demonstrated a connection between the coronary veins and the openings in the heart walls. His experiment—simple and convincing—consisted of blowing air into the coronary veins, with the heart immersed in water, and observing the bubbles of air escape through the openings in the heart wall. Since then these vessels have been known as Thebesian veins, but, as will be shown presently, Vieussens and Thebesius, though unaware of it, were dealing with different groups of vessels which were separated by the capillaries.

In 1798, Abernethy⁷ confirmed the results of Vieussens, and, while he did not fully appreciate the significance of his findings, his experiments demonstrated vascular communications between the chambers of the heart and the arterial side of the coronary circuit.

These interesting discoveries were lost sight of, and until the past score of years they have been ignored in almost all anatomical and physiological studies of the coronary system. Recently Kretz⁸ and more particularly Crainicianu⁹ began to recognize their importance. The latter

showed for the first time that the aggregate diameter of the luminal vessels was almost equal to that of the coronary arteries

In 1928,¹⁰ when we perfused the coronary arteries and collected the outflow from the coronary sinus and the chambers of the heart, we were astonished to find that approximately 80 per cent of the fluid escaped from the luminal vessels and only 20 per cent from the coronary sinus. It was natural, then, to ask ourselves what role these vessels might play in the circulation of the heart and what relationship they might bear to the arteries, capillaries, and veins. In work with S. R. Mettler in 1928 it was found that if a solution of celloidin too thick to penetrate capillaries was introduced into the coronary arteries some of it escaped by way of the luminal vessels into the chambers of the heart. In another experiment the ventricular chambers were filled with a solution of red celloidin. Suction applied at the ostia of the coronary arteries drew the celloidin into the openings of the luminal vessels. Blue celloidin was then injected into the coronary arteries where it fused with the red. When the muscle was digested off, casts of the arterial luminal vessels were revealed.

These vessels were also demonstrated by wax reconstruction. One of the openings of the luminal vessels in the ventricular wall from which the celloidin protruded was selected under the dissecting microscope and marked with India ink. The muscle containing this vessel was then cut into serial histological sections. Study and wax reconstruction of these sections, in collaboration with T. G. Klumpp and L. J. Zschiesche,¹¹ revealed two types of vessels which connected the arterial side of the coronary circuit with the heart chambers, one direct from the arterioles, and the other through the myocardial sinusoids directly into the chambers. The more direct arterio-luminal vessels are not numerous, but the arterio-sinusoidal vessels occur in large numbers and are easily recognized. Their structure, except for the irregularity of the lumen, is identical with that of the capillaries. It is quite possible, therefore, that the metabolic exchange through their walls is the same as that which occurs through the capillary walls.

The Thebesian veins are connecting channels between the capillaries and coronary veins on the one hand and the heart chambers on the other. This was shown in our laboratory in 1928, and the excellent work of Grant¹² has demonstrated the various branchings and communications of these veins.

Of the remaining larger branches of the coronary arteries the extracardiac vessels are worthy of note. First described by Albrecht von Haller in 1803,¹³ these vessels leave the heart around the root of the aorta and around the ostia of the superior and inferior venae cavae, and in the intervacular pericardial reflections. In work with C. L. Hudson and A. R. Moritz, 1932,¹⁴ they were shown to anastomose with the arteries supplying the aortic wall, the pericardium, the upper and lower surfaces of the diaphragm, the pleural surfaces of the lungs, the trachea and esophagus.

The capillaries of the myocardium are very difficult to recognize, indeed, in the ordinary histological section only an occasional capillary can be identified. In order to visualize the capillary bed, injection of dyes through the coronary arteries or veins must be resorted to. In the dead heart, however, the luminal vessels offer less resistance to the injection mass than do the capillaries, consequently, in most instances attempts to inject the capillaries via the coronary arteries fail, and the mass escapes into the heart cavities through the luminal vessels. Attempts to fill the capillaries through the coronary veins likewise fail because the mass escapes through the Thebesian veins. We found, in 1928,¹⁰ that if a heart can be revived by perfusing it with an oxygenated Locke-Rosenheim solution, the capillaries can be injected without difficulty by adding dye to the perfusate.

With the capillary bed visible it was an easy matter to trace its connections not only with the arterioles and venules, but with the sinusoids and Thebesian veins as well. As a result of these observations it is now possible to construct a diagram of the coronary circulation.

The coronary arteries, as shown in Figure 1, may communicate with extracardiac arteries, with ventricles through the arterio-luminal and arterio-sinusoidal vessels, and finally with one another. If there be any doubt of the existence of communications between the different trunks of these arteries, the preparations of Spalteholz¹⁵ and Gross¹⁶ should dispel it, for in the anatomical sense, at least, these workers have shown that the coronaries are not end arteries. Moreover, even in the event of complete closure of the ostia of the coronary arteries the heart still has access to a blood supply at arterial pressure levels through the extracardiac and arterio-luminal vessels. Two cases reported with Timothy Leary,¹⁷ in 1930, show that the heart is capable of sustaining an active life with the mouths of both coronary arteries occluded. Since reporting

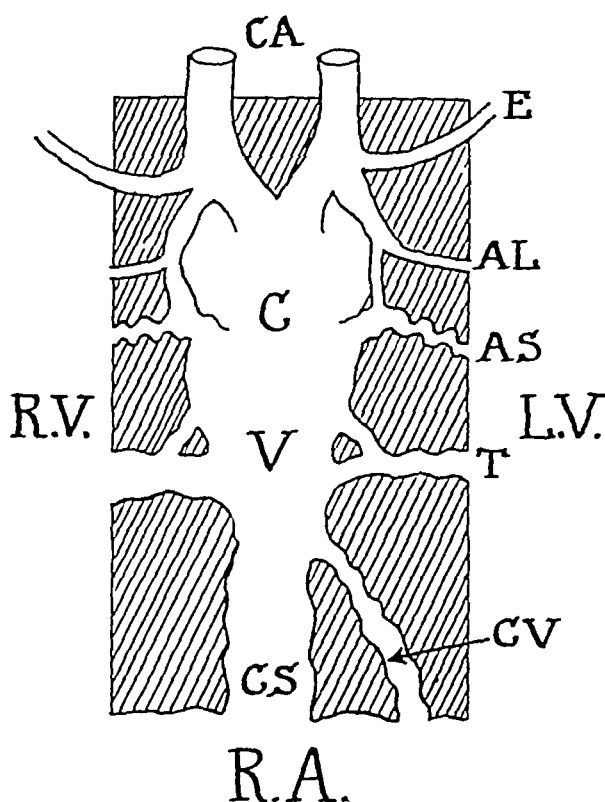


Fig 1

CA—coronary arteries
 E—extracardiac branches
 AL—arterio-luminal vessels
 AS—arterio-sinusoidal vessels
 C—capillaries
 T—Thebesian veins

V—coronary veins
 CV— " "
 CS—coronary sinus
 R V—right ventricle.
 R A—right auricle.
 L V—left ventricle.

these cases, a number of others with occlusions of one or both coronary arteries have been recorded. Despite the occlusion of whole arteries, infarction of these hearts did not occur.

The question naturally arises as to how these hearts get their blood supply. In the event of occlusion of the ostia of both coronary arteries one can only conclude that the arterial blood must come either from the extracardiac vessels or from the arterio-luminal vessels. But I know of no evidence that would indicate whether one or both of these sources are utilized. No other channels of sufficient size to supply enough blood to maintain normal heart action are known to exist.

In the event of the closure of the ostium or of a large branch of one

coronary artery, Schlesinger¹⁸ has shown that, if given sufficient time, anastomoses will develop from other branches of the artery. The work of Mautz and Beck¹⁹ on dog hearts would indicate that in these animals closure of one coronary artery results in marked enlargement of the already existing anastomoses. In their experiments a large branch of one artery was tied off in gradual stages. This gave sufficient time for the collateral anastomoses to develop. Supportive evidence is also found at autopsy, in instances where syphilitic aortitis or advanced coronary sclerosis may completely occlude one or both major branches of the coronary arteries without the production of infarction. One important factor should be pointed out at this time, and that is the factor of time. All of these processes require weeks, if not months or years, to bring about the gradual closure of the main trunks of the arteries, thus giving ample time for the existing anastomotic channels to begin to function.

The role that the luminal and Thebesian vessels play in the circulation of the normal heart has received very little attention. Evans and Starling,²⁰ Markwalder and Starling,²¹ Anrep and Hausler, 1928,²² and others have shown that part of the blood entering the coronary arteries does not return through the coronary sinus, and they have assumed, with Thebesius, that the luminal vessels serve only as auxiliary veins. These workers, unfortunately, did not observe pressures within the chambers of the heart, nor did their studies take into consideration the possibility of an ebb and flow of blood in the luminal vessels. The flow from the luminal vessels, under the conditions of their experiments, was constant at about 40 per cent of the coronary artery inflow.

Stella²³ found no flow from the peripheral ends when he cut the coronary arteries. His animals lived for two minutes at most after the arteries were cut, and the hearts failed instantly, so allowance must be made for the fact that these experiments were made on moribund animals.

Bohning, Jochim and Katz²⁴ injected killed cultures of staphylococci and hay bacilli and other particulate matter into the vena cava, under conditions which precluded entrance of the injected material into the coronary arteries. They found the bacilli in the capillaries of the heart wall, and concluded that the luminal vessels act as a source of blood supply in normal hearts.

Recently, Wiggers²⁵ has approached the question of the direction of flow of blood in the luminal and extracardiac vessels from a theoretic-

cal standpoint, taking into account the pressure relations and the pressure gradients available for flow through anastomotic channels, if they exist

Under normal conditions, the pressure gradients are such that a transfer of blood from the coronary arteries to the left ventricle could occur during the whole of diastole and during the early part of isometric contraction. In the right ventricle and auricles, on the other hand, the pressure gradients are such that a theoretical transfer of blood could occur throughout systole and diastole.

The practically identical pressures in the coronary arteries and extracardiac anastomoses would prevent any flow of blood between them at any time in the cardiac cycle.

If one examines the pressure relations that exist when the coronary ostia are occluded, as shown in the curves of Wiggers,²⁶ it is obvious that the pressure gradients are ideal for flow from the ventricle into the luminal vessels and sinusoids, but the answer to this question must await experiments not yet complete.

During the past two years, with Doctors D. E. Gregg, R. W. Eckstein, and J. T. Roberts, work* has been carried on in our laboratory with the purpose of finding out the direction of the flow in the luminal vessels in the right ventricle and the effect upon the flow of changing pressures within that chamber. By means of a shunting device with a two-way valve introduced into the pulmonary artery of a dog it was possible to allow the blood entering the pulmonary artery to flow through the device directly into the pulmonary arteries, as usual, or, by turning a cock, to shunt the blood from the right ventricle into a rubber balloon which, as it filled, displaced an equal volume of blood from the flask outside the balloon back into the pulmonary artery. In this manner Chicago blue or India ink was introduced into the right ventricle without the possibility of its reaching the lungs or the coronary arteries. During the experiment right and left ventricular pressures were recorded.

After introduction of the shunting device the pressures were allowed to become constant, with the blood flowing directly through the pulmonary artery. The usual pressures were about 100/7 in the left ventricle, and 19/2 in the right ventricle. Blood was then shunted into the balloon and India ink was introduced into the vena cava at such rate that

* This work and the metabolic studies reported later in this paper, were made possible by a grant from the Commonwealth Fund.

the right ventricular pressure was not changed. At the desired time the heart was stopped by the introduction of KCl or glacial acetic acid into the left ventricle. It was then fixed, sectioned, and examined microscopically for the presence of India ink in the vessels of the myocardium.

These experiments gave convincing evidence that the pressure gradient between the right and left ventricles determined the direction of flow in the luminal vessels of the right ventricle. So long as the pressure in the left ventricle was greater than that in the right, no significant flow took place from the ventricle into the luminal vessels. There was an occasional superficial vessel in the septum that contained ink, but these extended less than 2 mm below the endocardial surface. The capillary bed, by gross and microscopic examination, was free from injection mass.

If, at the time of injection of the ink, the right ventricular pressure was greater than the left, a very significant flow took place from the ventricle into the luminal vessels, as evidenced by a complete injection of the capillaries and larger vessels. When the capillaries were filled with ink the heart was grossly black, and this observation was utilized in a third experiment. In the beginning, with the left ventricular pressure definitely higher than the right, an injection of ink into the vena cava was begun. The heart remained red in gross appearance—evidence that the ink was not entering the myocardial vessels from the ventricle. The pressure relations were then changed by raising the right ventricular pressure and lowering that in the left ventricle simultaneously. As the pressures became equal the ink began to enter the luminal vessels and the heart turned black the instant that the right ventricular pressure exceeded that of the left. Inasmuch as these observations were made in the intact animal, the conclusion is drawn that there is no flow of blood from the right ventricle into the luminal vessels, under normal conditions.

Support is given to these results by the following experiments in rabbits. If Chicago blue is injected into the right ventricle of a normally beating heart at a pressure insufficient to raise the right ventricular pressure to that of the left ventricle the heart turns blue only after the dye has passed through the lungs and entered the myocardial capillaries via the coronary arteries. If, after injection of the dye into the right ventricle, the heart is allowed to beat two or three times and at this point the right ventricular wall is suddenly opened with a pair of scissors near the pulmonary artery, the right ventricular pressure drops to zero and

the dye never reaches the left ventricle. Microscopic examination reveals no dye in the myocardial vessels.

The normal function of the luminal vessels in the left ventricle is unknown.

CAPILLARY BED

The normal relationship of the capillaries to the muscle fibres which they supply with blood is of considerable importance. They communicate freely, not only with arterioles and venules, but equally with all the luminal connections. Thus, the muscle fibres enjoy several possible sources of blood supply. It has long been known that at the time of birth the muscle fibres are small in diameter. During physiological growth the fibres increase in diameter and length, thus increasing the thickness of the heart wall, the capacity of its chambers, and the total heart weight. There are also concomitant changes in the blood vessels of the heart. Ehrlich, de la Chapelle and Cohn,²⁷ for instance, found that the arteries of each ventricle increase in direct proportion to the weight of the ventricles.

The muscle fibres, the capillary bed and the quantitative relationship between the two were studied in our laboratory during growth, in rabbits and in man, in 1937, in collaboration with R. A. and L. J. Shipley,²⁸ and during the past three years in human hearts, with J. T. Roberts.

Certain precautions are necessary in studying quantitative changes in muscle fibres and capillaries. First, a method of fixation and mounting the histological sections must be used which will avoid the errors that result from shrinkage. Secondly, accurate determination of the number of capillaries depends upon complete injection of the capillary bed in the section of tissue studied. In our hands, this has been uniformly successful only in those hearts which were revived and injected while beating. In only a few instances have successful injections been made by other methods in hearts obtained more than six hours postmortem.

At the time of birth, in the rabbit heart, there was one capillary for every five or six muscle fibres. The capillaries were evenly distributed and ran parallel to and alongside the fibres. In the human heart the same relationship was observed. In the heart of a seven months' fetus there was one capillary to six muscle fibres, while in the heart of an infant ~~three-weeks~~ old, the ratio was four fibres to each capillary.

the increase in diameter of the muscle fibres as a result of

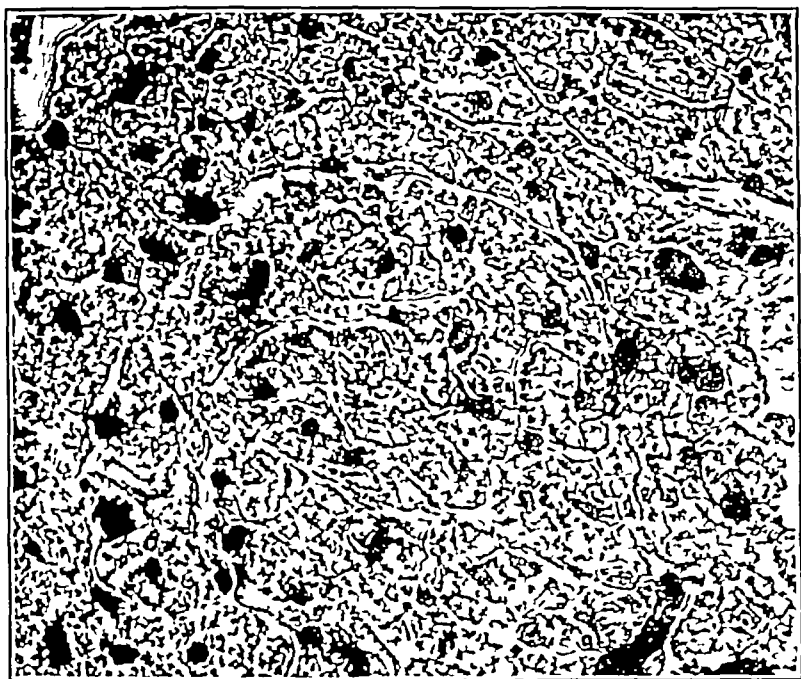


Fig 2—Heart of infant (3 wks) Note small fibres

growth, the fibre-capillary relationship began to change, so that in the heart of a child sixteen years of age there was one capillary for two muscle fibres. This change in the ratio of fibres to capillaries continued until growth was completed, at which time the ratio of fibres to capillaries was approximately 1:1. We have relatively few observations on the hearts of growing rabbits and of children, with no children's hearts between the ages of one and eight years, but, as will be seen in Figures 4 and 5, the curve of the fibre-capillary ratio in the human heart is almost identical with that in the rabbit heart. Moreover, this curve seems to take the form of a hyperbole, which is a form frequently observed in growth phenomena.

Once growth is completed, the fibre-capillary ratio remains constant, at approximately 1:1, so long as the heart remains normal, both in man and in the rabbit.

In a group of twenty-six normal hearts of adults the fibre-capillary ratio ranged from 0.97 to 1.68, with an average of 1.34 (± 0.023). The remarkable uniformity of this figure throughout the group is in sharp

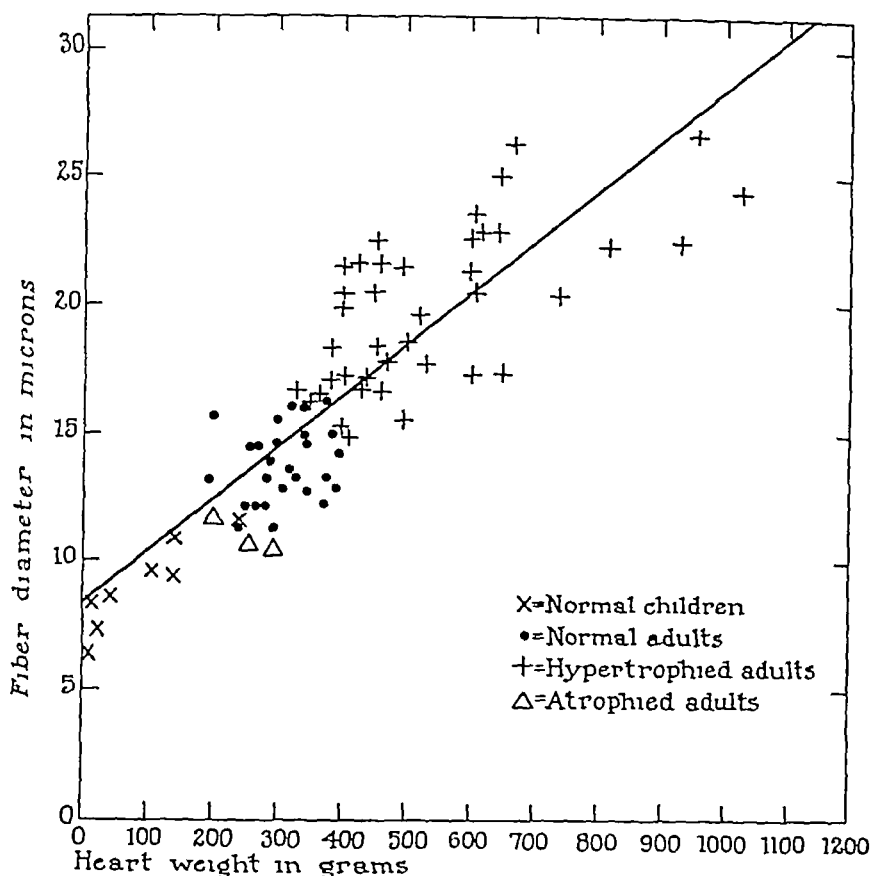


Fig 3—The influence of growth, hypertrophy and atrophy on fibre diameter

contrast to the constantly changing one during growth

It has been claimed by Tangl²⁹ that the increase in fibre diameter during growth may be as much as six-fold. Our observations show an increase in human hearts during growth of five-fold. Findings in the rabbits were of the same order. Thus, the one capillary which at birth supplied five muscle fibres, in the adult supplies one fibre, the area of which is approximately that of five fibres at birth.

In view of the increasing mass of muscle and the changes in the fibre-capillary ratio during growth, it is interesting to observe the effect of this change upon the concentration of capillaries in a square millimeter of heart muscle. In the human heart at birth there were approximately 4000 capillaries per square millimeter. This concentration remained essentially the same in children's hearts throughout the period of growth, the average for all children's hearts being 3700. The same constancy was

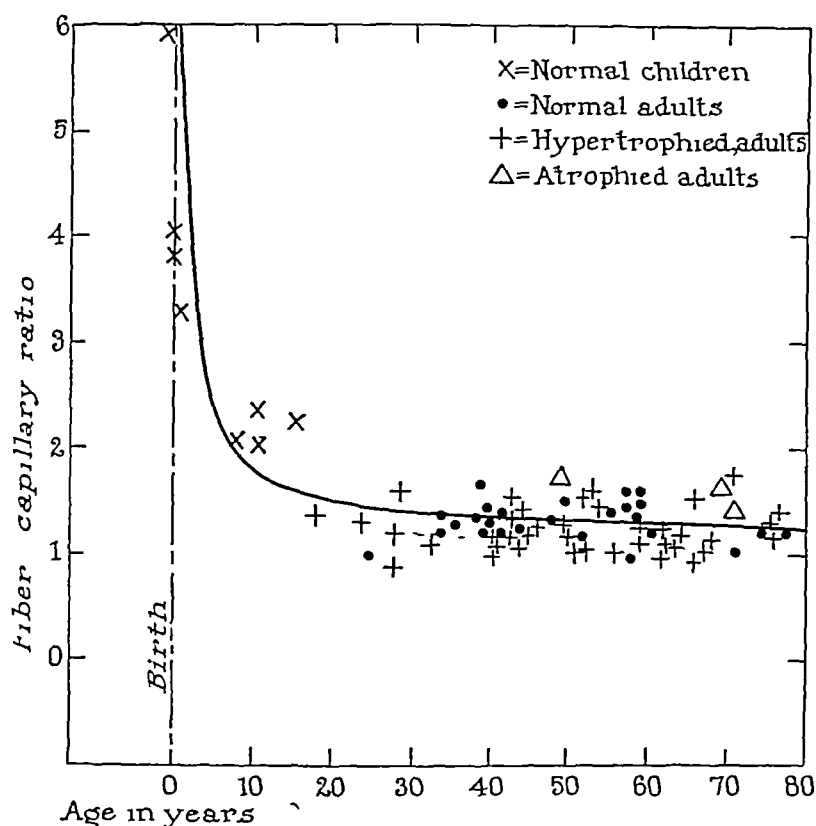


Fig. 4—The influence of growth, hypertrophy and atrophy on the number of fibres per capillary

found in the concentration of capillaries in the rabbit hearts

The changes occurring during growth of the heart may be summarized as follows. At birth there are five muscle fibres to each capillary. As the fibres increase in size the fibre-capillary ratio changes constantly until there is approximately one capillary for each muscle fibre. Throughout the growth period the concentration of capillaries per unit of area is maintained at a constant level. It is obvious, therefore, that the increase in muscle mass is accompanied by a corresponding increase in the total number of capillaries.

In the normal hearts of adults the capillary concentration also remains remarkably constant. In the twenty-six hearts with an age range from twenty-five to seventy-seven years, the number of capillaries per square millimeter ranged from 3000 to 4000, with a mean of 3342 (± 36). The standard deviation for the entire group was only eight

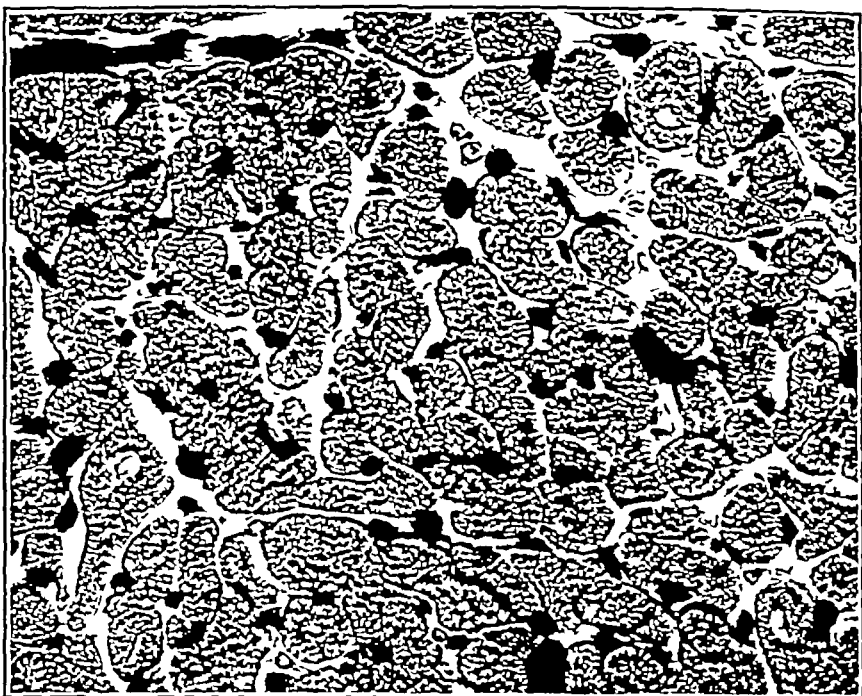


Fig 7—H 30 Wt 300 gm Capillaries 3551 per sq mm Fiber diam 15.5 micra

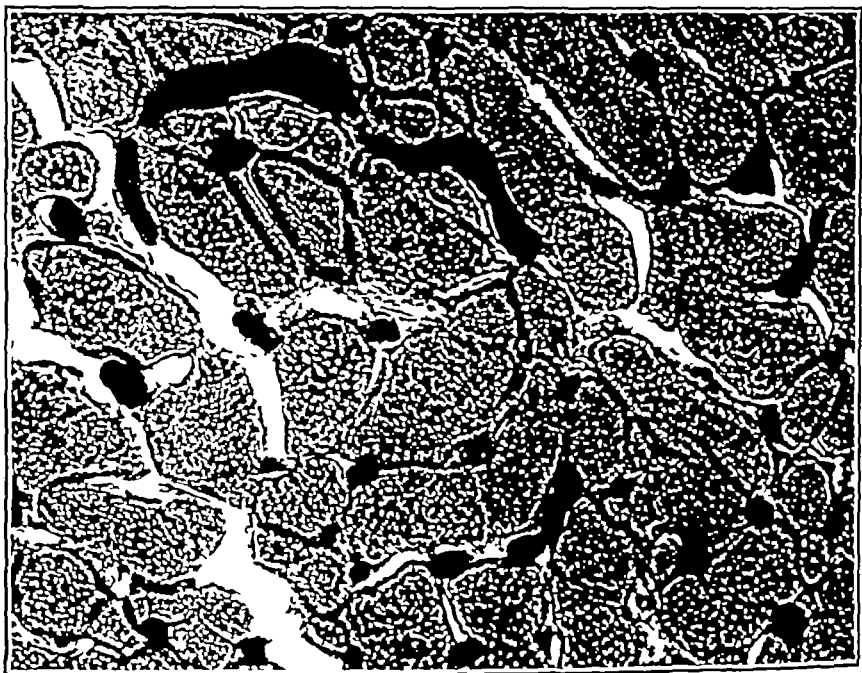


Fig 8—H 52 Wt 930 gm Capillaries 2251 per sq mm Fiber diam 22.1 micra

the majority of these patients

The degree of hypertrophy varied considerably. Some of the hearts showed so little enlargement that they might well have fallen within the normal group. At the other extreme was a heart weighing 1150 gm. The average weight for the group was approximately 525 gm (± 161).

During hypertrophy the muscle fibres increased in size throughout the heart. The enlargement was in almost direct proportion to the increase in weight of the heart. In many instances some of the fibres reached diameters triple those of normal heart fibres.

Despite the marked increase in size of the fibres, the fibre-capillary ratio showed practically no change. The ratio of approximately 1:1 was as uniform in this group as in the normal hearts.

The most striking change found during hypertrophy was observed in the concentration of capillaries in the muscle. As the muscle fibers increased in diameter the capillaries were pushed farther apart, and this resulted in a decrease in the concentration of the capillaries per unit area of muscle. The concentration of the capillaries diminished in proportion to the increase in the fibre diameter and to the increase in heart weight. Thus, the larger the heart, the less the concentration of capillaries.

With these data concerning growth and hypertrophy in hand it becomes clear that they are separate and distinct processes. Growth of heart muscle is accompanied by a proportional increase in the number of capillaries, while hypertrophy of the muscle results in an actual decrease in concentration of capillaries. It would avoid a great deal of confusion if we reserve the term "hypertrophy," as applied to hearts, to those that show changes in keeping with this definition. The much discussed increase in size of the hearts of young athletes is frequently spoken of as hypertrophy. But whether it is actually hypertrophy or growth can be settled when such hearts are subjected to the type of study just described.

ATROPHIED HEARTS

Three hearts, atrophied as a result of wasting disease, were studied. The muscle fibre diameter decreased and the capillaries moved more closely together, resulting in an increase in the capillary concentration.

In all quantitative measurements of muscle and capillary-muscle relationship which have been described up to this point our observations

TABLE I

	AV HEART WT	MEAN AGE	AV HT WT BODY WT RATIO	AV FIBRE DIAM	AV NUM- BER CAP- ILL. PER SQ MM	AV FIB./CAP RATIO
	<i>gm</i>			<i>mu</i>		
Child*	20	3 wk	0.0069	7.4	4513	4.04
Normal adult	310	51	0.0054	13.9	3342	1.34
Hypertrophv	535	49	0.0088	19.8	2483	1.23
Atrophv	247	66	0.0043	11.1	4613	1.69

* Single heart for comparison

were confined to muscle bundles of myocardium in order to obtain an accurate picture of the functioning muscle. Recently, we have studied some of these hearts in a different manner. The same measurements were made, but instead of confining the observations to muscle bundles, cross sections of the whole heart tissue were studied so as to include scars, large fibrous septa lying between muscle bundles, etc. A comparison of these results with those obtained from the study of the muscle revealed in some instances some interesting results.

In the hypertrophied hearts the inclusion of counts on the whole tissue caused a marked drop in the total capillary concentration, sometimes to less than half that in the muscle bundles.

Microscopical studies of the scarred areas in the hypertrophied hearts showed a marked disturbance of the muscle-capillary relationship. Muscle fibres were frequently partially or completely surrounded by scar tissue, and fibres in various stages of degeneration were found. The important point, from our viewpoint, was the fact that many of these fibres were without capillaries. In many fields, also, the capillaries were fairly evenly distributed in the scar tissue where the fibres had completely disappeared.

It is obvious that the efficiency of fibres without capillaries and of capillaries without fibres in performing their respective functions might be seriously interfered with.

With the guidance and help of Professor J. R. Musselman of the Department of Mathematics of Western Reserve University we have studied the data of the quantitative relationship of the capillaries to the muscle mass. It was found that a high order of correlation exists—so

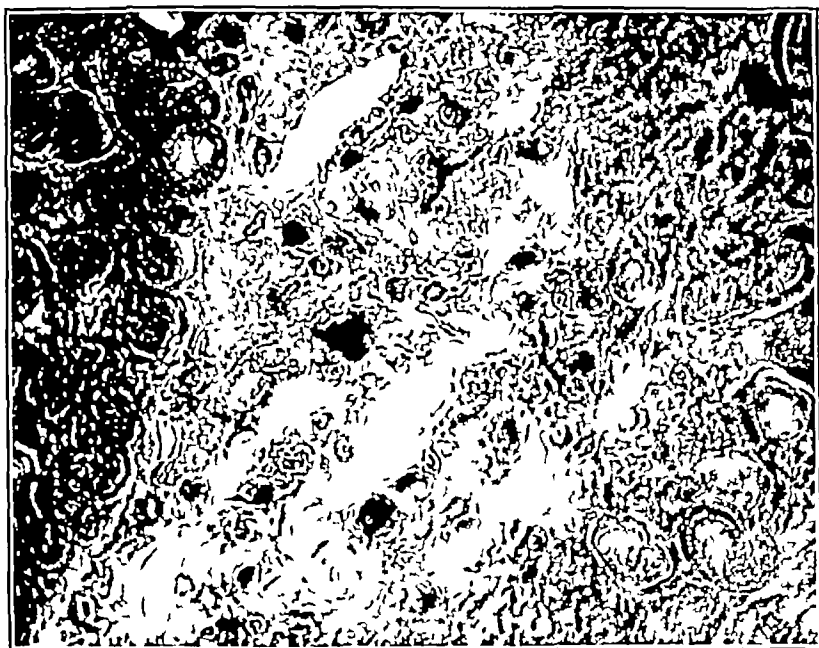


Fig 9—Scar in myocardium (rheumatic fever) showing distribution of capillaries

high at times that it suggests the possibility of a governing biological law. There is, for instance, a practically perfect positive correlation between the heart weight and the average muscle-fibre diameter. Thus, if the heart weight is known, the average muscle-fibre diameter can be calculated with a probable error for the predicted value of ± 1.435 μ .

Likewise, between the average fibre diameter and the number of capillaries per sq mm there is a close correlation and, if the fibre diameter is known, the capillary concentration can be calculated with a probable error for the predicted value of ± 209 capillaries.

As a result of these two correlations, the expected correlation between the heart weight and the capillary concentration was found to exist, so that, given the heart weight, the capillary concentration can be calculated.

And, in similar manner, the fibre-capillary ratio can be predicted from the patient's age.

One can also calculate the capillary surface area available for the diffusion of oxygen and the exchange of metabolites in a cubic centimeter of muscle. This was found to be

Hearts of children	1145 sq cm.
Adults (normal)	1184 " "
Hypertrophied	623 " "

When this ratio is plotted against the heart weights (Chart V), the hearts of children and normal adults show the same wide range, without apparent correlation to heart weight. The hypertrophied hearts fall well below the range of the normal hearts and show a definite rectilinear negative correlation of high degree with the heart weight. Thus we interpret as showing that, in the normal hearts of children or adults, the capillary surface per cubic centimeter of muscle is constant and independent of heart weight.

At this point the temptation to speculate is almost irresistible. Our observations on the changes during hypertrophy show that, as the heart enlarges, the distance from the capillary wall to the periphery of the muscle mass which it supplies becomes greater. This means that the route over which oxygen has to diffuse and metabolic products have to travel increases in proportion to the degree of hypertrophy. Moreover, the actual capillary surface available for exchange is markedly decreased per cubic centimeter of muscle. It seems safe to say that at some stage in the course of hypertrophy a point will be reached where metabolic exchange will be seriously interfered with.

Chemical studies designed to find out whether hypertrophy interferes with the exchange of metabolites are not yet sufficiently advanced to answer this question, but a few observations have been completed and are perhaps deserving of brief mention.

The oxygen utilization by the heart muscle has, in the past, been studied, for the most part, either in isolated hearts or heart-lung preparations. Katz and Long³⁰ have shown that skeletal muscle can establish an appreciable oxygen debt without harm, whereas heart muscle in the same animal can tolerate very little oxygen debt. Indeed, any appreciable diminution in the oxygen in the arterial blood reflects itself immediately in the weakening of the heart beat.

Oxygen, of course, is required for the removal of lactic acid, and it was shown by these workers, as well as by others, that the heart tolerates only about one-quarter of the lactic acid concentration that skeletal muscle does. The heart, therefore, is dependent upon its contemporary oxygen supply in order to function efficiently.

Hastings and Blumgart³¹ have recently found that brief periods of

TABLE II
Coronary arterial-venous oxygen difference in dogs

OXYGEN CAPACITY	OXYGEN CONTENT					
	Arterial		Coronary vein		Femoral vein	
vols %	vols %	% sat	vols %	% sat	vols %	% sat
15.1	12.7	84	2.6	18	12.3	82
17.6	16.1	92	3.1	18	12.8	73
18.1	17.6	97	9.8	53	13.3	74
20.7	20.2	98	5.0	24	15.3	74
19.8	18.8	95	6.2	31	13.1	66
15.5	12.5	81	3.6	23	7.8	50
23.1	21.0	90	3.7	16	15.7	67
21.8	19.1	88	2.8	12		
21.2	18.1	85	2.6	12		
22.1	17.2	79	3.3	15		
23.5	20.5	88	3.7	16		

anoxemia produce measurable chemical changes in heart muscle, in the absence of histological change

In work now in progress with J W Price and D E Gregg, the oxygen utilization of the normal heart is being determined in the dog. With the animal anesthetized and, therefore, at complete rest, blood samples have been collected under proper conditions and as nearly simultaneously as possible, from the left ventricle, the coronary sinus, and in some instances from the femoral vein.

The percentage saturation of oxygen in the venous blood from the coronary sinus was constantly and surprisingly low. The figures ranged from 12 per cent to 53 per cent, with an average of 23 per cent, whereas the average saturation of the femoral venous blood was 70 per cent.

The following experiment illustrates the methods used. The heart was exposed under sodium pentobarbital anesthesia with artificial respiration. In some instances the chest was closed and made air tight by means of the pericardium, which was sewed to the walls to form a cradle in which the heart could beat outside the chest. This procedure also enabled the animal to breathe normally. Care was exercised to avoid tension on the vessels and nerves at the base of the heart. Each set of three blood samples was taken within a period of five minutes. The following results from one experiment are typical.

DATE	CORONARY VEIN			RIGHT VENTRICLE			LEFT VENTRICLE		
	O ₂ content	O ₂ capacity	Saturation	O ₂ content	O ₂ capacity	Saturation	O ₂ content	O ₂ capacity	Saturation
	vols %	vols %	%	vols %	vols %	%	vols %	vols %	%
2/15/40	4.6	21.8	21	14.8	21.7	68	21.3	21.8	98

TABLE III

Percentage O₂ saturation

	ARTERIAL	VENOUS	
Himwich & Castle	92-108 av 99	12-64 av 38	Gastrocnemius, exercised
Barcroft & Kato		51-70	"
Price, Gregg & Wearn	79-97	12-53 av 23	Heart anesthetized dog

Oxygen capacity was determined on each blood sample and each percentage saturation value was calculated from corresponding content and capacity values.

Barcroft and Kato, in 1915,³² and Himwich and Castle,³³ in 1927, determined the O₂ utilization in the resting and exercised leg muscles of dogs. A comparison of their findings with ours is shown in Table III.

From these figures it is obvious that percentage saturation of the venous blood of the heart of a dog at rest is significantly lower than the venous blood from exercised skeletal muscles. The heart, in what might be called a resting state, therefore, leaves very little oxygen in the coronary venous blood.

This almost complete use of available oxygen by the normal heart offers a plausible explanation for the findings of Katz and Long that the heart will not tolerate an oxygen debt. It also suggests that any increase in work by the heart must be met by an increase in the coronary blood flow, which could be brought about either by the opening of additional capillaries or by an increase in the velocity of the flow of blood in those capillaries already open.

In regard to the opening of additional capillaries it may be said that in numerous experiments in our laboratory we have never been able to demonstrate an intermittence of flow in the capillary bed of the myocardium, nor has any convincing evidence of intermittence ever been published, of which I am aware. Our work is still in progress, but it seems very likely that the heart uses all of its capillaries at all times. The mechanism available, therefore, for meeting strain is most probably an increase in blood flow in the coronary circuit.

It is now generally accepted that the muscle pigment also plays a role in oxygen transfer and storage. Whipple³⁴ and his co-workers³⁵ have shown that myoglobin, or muscle hemoglobin, is present in the myocardium of puppies to the extent of 100–200 mg per 100 gm of muscle, increases to 300 mg at puberty, and reaches 300–400 mg in adult dogs. They showed that exercise or activity can increase the amount of pigment in the myocardium and the lowest values were encountered in the most inactive animals.

Hurtado et al.³⁶ observed that dogs kept at high altitudes in the Andes have more myoglobin than dogs kept at sea level. This finding was interpreted as an adaptation to facilitate O₂ exchange in the face of chronic anoxemia.

In view of the increase of myoglobin in heart muscle during normal growth and during the chronic anoxia of high altitudes, we have begun observations upon the muscle hemoglobin in normal and hypertrophied human and rabbit hearts. While our data are too few to justify final conclusions, we have found, thus far, no appreciable difference in the myoglobin content of normal and hypertrophied hearts of rabbits or man. These results are in keeping with those of Cowan and Bauguess,³⁷ who found no increase in myoglobin in hypertrophied hearts in rats. If these findings prove to be constant they will represent another fundamental difference between the process of hypertrophy and that of normal growth.

Several changes occur in hypertrophy, therefore, which at some stage of the enlargement will impede oxygen diffusion and the exchange of metabolites. At what point during the process of hypertrophy and to what extent they interfere must await further study of the metabolites with a simultaneous measurement of the flow of blood in the coronary arteries.

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EFFORT, TRAUMA, OCCUPATION AND
COMPENSATION IN HEART DISEASE*

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BECAUSE of the frequency of heart disease the question of compensation in relation to it has always been an important problem, and it is even more so today as a result of a great increase in the number of workers employed in the national defense program

For a number of years my colleagues and I have been especially interested in the role of effort, work and trauma in various heart diseases and have collected data on this subject¹ Tonight I should like to state my conclusions concerning compensability in the main conditions of the heart I have been seeing compensation cases over a period of ten years but their number forms only a small part of my medical practice This has enabled me to avoid the error of the man doing only compensation work who tends to think that effort and trauma play a role in every disease and the error of the man who does not interest himself at all in compensation and believes that it offers no problem

As a physician I am concerned here with the medical aspects of the problem and not with the numerous legal ramifications which may attend individual cases In each case the following questions should be considered (1) Was the stated effort, occupation or injury capable of producing the symptoms of the patient or the damage in the heart found on examination? (2) Was heart disease present prior to the strain or accident? The latter may have aggravated a preexisting heart condition or may have been coincidental (3) If the strain or injury has damaged the heart, how long will this effect persist? Usually symptoms referable to effort or trauma last a relatively short time, that is, hours, days, weeks or at most several months If symptoms persist, or appear, later than this, they may be related to the antecedent heart disease, and not to the exertion or injury

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The problem requires careful consideration and must be approached with an unbiased mind. A good general rule to remember is that the interval between an effort or accident and the onset of symptoms is usually short, the latter are delayed in only a few instances.

In the course of my talk I shall illustrate my point by citing short case reports. I wish to emphasize the fact that I shall purposely omit those in which a relationship to effort or trauma is obvious and readily admitted. I shall quote only those cases referred to me as heart conditions causally related to effort and trauma, but in which I think any association was dubious or not present.

Hypertension and Arteriosclerosis In spite of the very extensive experimental work performed in the past few years the cause of ordinary high blood pressure or essential hypertension, that is, the type not due to obvious kidney disease, remains obscure. We know that there is a familial tendency and a frequent association with obesity and glandular disturbances. It is a chronic condition which comes on gradually and often without symptoms, and is not compensable. This applies also to enlargement of the heart and hardening or sclerosis of the arteries, both of which result from or accompany high blood pressure. Cardiac enlargement and arteriosclerosis develop over a period of years and cannot be related to any particular event or effort. Incidentally the term "chronic myocarditis," which has been applied loosely to this type of heart disease, should be discarded. Instead one should specify chronic disease of the coronary arteries with scarring or fibrosis of the heart muscle. When high blood pressure and hardening of the arteries have become developed after a number of years, several complications may occur.

"Stroke" A "stroke" may be produced in three ways. The commonest is rupture of a small artery in the brain resulting in hemorrhage. Secondly, a clot or thrombosis may form locally in a small blood vessel. Thirdly, a clot may be dislodged from a diseased heart and an embolus may settle in the brain. All three of these result in damage to brain tissue and may be followed by loss of consciousness, paralysis, etc., which may be very brief in duration or may persist. I believe that the third type, namely, dislodgement of a clot from the heart is probably not related to effort. The relation of cerebral hemorrhage and thrombosis to strain, however, is not definite. The general opinion is that they are due to hardening of the arteries and occur independently of effort, but

or illness before lifting a thirty-five pound bolt of cloth, following which he experienced an attack of pain I saw him three years later and he claimed that since that attack he had felt pain over the heart whenever he exerted himself In spite of repeated questioning he was firm in his statement that he had never felt any pain prior to the effort described Yet two physicians testified that he had experienced heart attacks with pain three years and two years before the effort, during one of which he had been in a hospital, and that several confirmatory electrocardiograms had been taken I too, found on examination that this man had had heart trouble for many years Therefore, only the attack of pain immediately following the lifting of the bolt of cloth was compensable, and only for a short time, the pain over the heart during the following years, like that prior to the exertion, was associated with his long-standing heart disease and was unrelated to the effort described This experience is quite a common one not only in my own practice but, I am sure, in that of other physicians

Coronary Occlusion or Thrombosis This is THE heart attack, which is characteristic and usually easy to diagnose It also produces typical changes in the electrocardiogram It occurs most often between the ages of 50 to 60 years, but one-third the cases are under 50 The great majority of patients have had high blood pressure and angina pectoris due to coronary disease About three and one-half times as many men as women sustain an attack The latter is the result of a sudden complete obstruction of one of the coronary arteries by a clot This cuts off the blood supply to a large area of the heart and death of the affected muscle occurs, a condition called cardiac infarction It is agreed that a clot does not form in a coronary artery unless that artery is already hardened or diseased

Effort and Coronary Occlusion In a series of 1700 attacks of coronary occlusion² detailed histories have revealed that the attack was not related to effort, excitement, occupation or other external factors, for it began practically always during sleep, rest or some routine activity The attack occurred during or directly after unusual strain in only 2 per cent This is an insignificant figure since all of us exert ourselves at least several times a day and if effort were a factor in precipitating coronary occlusion, the majority of attacks would be associated with exertion Coronary occlusion would therefore be far more common than it is

Recently one author³ has reported two cases in which a heart attack

occurred while playing baseball. One man of 45 stumbled and fell on his buttocks while batting at ball and had the attack. Another man of 43 slipped while playing ball and had the attack as he tried to right himself. The author, in all seriousness, attributed the heart attack in each case to the mishap. Surely if such slight exertion were capable of inducing a heart attack it would be unsafe for any person over 40 or 45 years of age to do much more than remain quiet or at most walk slowly.

Another point against attributing any influence to effort in the onset of coronary occlusion is the fact that in the 1700 cases studied almost 100 of the attacks were sustained by persons who had been in bed for considerable periods suffering from a chronic ailment such as lung abscesses, cancer, heart failure. Certainly the problem of exertion does not arise in this group.

Occupation and Coronary Occlusion Occupation did not play any role in coronary occlusion for in our series of 1700 cases it occurred in all types of occupation and professions and in all strata of society. Furthermore, we divided our cases into three groups, laborers and workers, storekeepers and business men, and professional persons, and found that the proportion of each of these groups was practically the same as in the general population of New York City.² Thus, coronary occlusion is just as apt to occur in the executive sitting behind a desk or even retired as in the longshoreman lifting heavy weights. Obstruction of a coronary artery takes place in the natural course of coronary artery disease, and, as we have shown, is not caused by exertion even if the latter is unusual. Surely it is not related to ordinary activities performed every day. Yet, I have been asked to examine cases in which coronary occlusion was attributed to such routine occupational activities as running an elevator (M B 8418), blocking hats (S S 7545), working at a small punch press (P S 7642), a mail dispatcher (D S 7823) lifting a twenty-five pound bag, a common performance in his job, carrying two bundles totaling twenty pounds (A G), a milkman (N S 9518) walking up a flight of stairs with only four quarts of milk in a container, he had been doing much harder work for twenty years. All of these men had had heart disease for many years and the heart attack or coronary thrombosis was part and parcel of this process, not affected by external factors such as work.

Mechanism of Coronary Occlusion Our conclusion that effort does not play a role in coronary occlusion is based on clinical data in a very

large series of patients. On the other hand, largely on theoretical grounds, some writers have stated that coronary occlusion can be precipitated by effort. They base this opinion upon recent pathological studies showing that in the natural course of arteriosclerosis, that is hardening of the arteries, hemorrhages form in the lining of the arteries, and that such an intimal hemorrhage in a coronary artery often initiates the formation of a clot or thrombus. Their reasoning is that unusual effort and excitement produce a rise in blood pressure or directly result in the hemorrhages just mentioned. This is purely speculative since there is no evidence at all for it.⁴ As a matter of fact, a number of observations point against the validity of such a theory. We have found these hemorrhages just as frequently in persons without elevated blood pressure and in patients who have been bed-ridden for weeks or months, as in persons who have high blood pressure and who exert themselves. Moreover, Winternitz⁵ injected fluid into the coronary arteries of men dying from heart disease under the unheard of pressure of 500 to 1000 mm Hg without producing these blood vessel ruptures. It seems clear that elevation in blood pressure is not the cause of these. It would be no more reasonable to assume that the destruction of red blood cells in the body, which is a natural, physiological process going on all the time, was the result of effort or was influenced by it.

The Premonitory Phase of Coronary Occlusion In the few bona fide cases in which a heart attack occurred during unusual exertion or excitement the relationship was coincidental. We have calculated that 500,000 attacks of coronary occlusion occur annually⁶ and it is natural that a number of them take place during work. It takes time for the occlusion to form⁷ and in these patients the final obstruction happens to take place in the course of their work but it is not brought on by it. This concept explains the observation of lesser degrees of pain several days or even weeks prior to the acute attack. During the premonitory stage the patient usually is well enough to continue working, and, if he performs some unusual exertion, he is apt to feel pain or the severity of the occlusion may be increased. But I repeat that the occlusion had already been in the process of formation and its completion is unrelated to effort. We have had the opportunity of observing a number of patients during the premonitory phase and have put them to bed. In spite of this they went on to develop the complete attack after several days or weeks. Thus, S. C. No. 9587, a man of 65, had sustained heart attacks

nine and seven years before, but had been free of pain since then. Several weeks previously he began to complain of frequent chest pain. I saw him after several days and suspected that a coronary occlusion was in the process of formation. Accordingly, I put him to bed, in spite of which he suffered a typical acute heart attack three days later.

In summary, we have shown that coronary occlusion is not produced by effort since it occurs almost always in the absence of unusual strain and just as often in those whose work is very light as in those who do manual labor.

Cardiac Infarction Without Coronary Occlusion. Acute Coronary Insufficiency. At this point I wish to emphasize that I have been speaking of the classical heart attack, that is, coronary occlusion or thrombosis, in which an obstruction forms in one of the coronary arteries and results in destruction of a certain area of heart muscle, a condition termed infarction. The latter can also occur without obstruction of a coronary artery. For example, when the coronary arteries are hardened or sclerotic, they are too narrow to permit an increase of blood to flow through them which is required when the patient exerts himself or becomes excited. As a result of not receiving enough blood and oxygen the muscle becomes necrotic or infarcted. This results in pain and even in death. This condition is called coronary insufficiency with infarction or necrosis of the heart and usually can be distinguished from coronary occlusion or thrombosis with infarction.⁸ Unlike the latter it may in certain instances be caused by effort, excitement and trauma and therefore is compensable. I shall cite a case to illustrate coronary insufficiency with necrosis or infarction of the heart muscle, without complete coronary artery obstruction.

M. M., a woman of 72, was attempting to cross a busy thoroughfare but was frightened back to the curb by a passing automobile which did not quite touch her. Soon after reaching the sidewalk she collapsed and by the time an ambulance had arrived she was dead. At necropsy the medical examiner found a severe degree of chronic heart disease but no acute thrombosis. In this case the fright increased the demand of the heart muscle for blood but this could not be supplied. Incidentally, if the automobile had injured the woman, no matter how slightly, the death would have been attributed to trauma. This emphasizes the necessity of exercising great care in compensation cases.

Operation and Coronary Occlusion. Several years ago we drew at-

tention to the fact that an operation, even if minor, may be followed by heart involvement. This is usually due to coronary insufficiency but in some cases it is possible that coronary occlusion is induced by operation. Thus A. M. No. 8706, 39 years old, injured his finger at work and it became infected. After some time it was incised and three nights later he sustained a heart attack. There was no history of heart symptoms at any time prior to the operation and it is possible that the latter was causally related to the attack.

Rheumatic Fever and Chronic Cardiac Valvular Disease Rheumatic fever is really a disease of the heart. Its cause is unknown but the onset is often associated with a sore throat or cold. The first attack usually occurs in childhood or adolescence and recurrences are very common. Severe effort has been considered by some a competent cause of a recurrence of rheumatic fever but in the cases in which the question of such causal relationship has arisen I have not been convinced of such an association. I may mention the case of a workman S. R. No. 9245, a man of 35, in whom many joints became inflamed following a fall. These seemed to be related until it was discovered that he had come to work limping prior to the fall. It is most likely that the joint inflammation had been present before the injury.

During the acute stage of rheumatic fever there is an acute inflammation of the lining of the heart valves, i. e., endocarditis, and of the heart muscle, that is, myocarditis. In most cases a chronic deformity of the valves, i. e., chronic cardiac valvular disease gradually takes place over a period of months or years, causing leakage through the valves and resulting in enlargement of the heart and murmurs audible to the examiner. All these are progressive changes in the course of rheumatic fever and cannot be ascribed to any external event. If a murmur is discovered following some unusual strain it is almost certain that the murmur antedated the exertion by many months at least, even though the patient was unaware of any trouble in his heart. We have already pointed out that in chronic heart disease heart failure is usually associated with infection. This applies particularly to rheumatic heart disease, but in rare instances heart failure may come on acutely following severe strain.

Syphilitic Heart Disease Syphilis often results, after a number of years, in deformity of the aortic valve of the heart or in disease of the large artery leaving the heart, namely, the aorta, in which a bulge or

aneurysm may form. These changes are due solely to the syphilitic infection and not to any external factor such as occupation, effort or trauma. The disease of the aorta and aortic valve usually comes on very insidiously and gives rise to symptoms only after the lesion is fully developed. Therefore, when some specific event or effort is more or less coincidental with the onset of symptoms it seems natural to the patient to attribute these to the effort or accident, whereas actually the underlying condition had been present for many years. We have seen that this applies as well to cases of coronary artery and rheumatic heart disease. Although a syphilitic aneurysm of the aorta is not produced by effort or trauma, the question arises whether these may cause rupture of such an aneurysm which is already present. It is possible that severe trauma may do so but I believe that effort does not. My remarks apply as well to aneurysm of the aorta produced by rheumatic fever and arteriosclerosis.

Dissecting Aneurysm of the Aorta There is another type of aneurysm of the aorta called dissecting aneurysm of the aorta. It is a rare condition that occurs as a result of advanced hardening and degeneration of the medial wall of the aorta, usually in association with high blood pressure. Because of the latter it has been claimed that the process may be initiated by some unusual exertion, or that the latter causes rupture and fatal hemorrhage. I believe, however, that this occurs at rest or during sleep more frequently than during exertion and may be independent of these or other outside influences.

Trauma of the Heart The heart and large blood vessels definitely may be traumatized as a result of external injury, and, indeed, it is remarkable that the heart is not involved much more commonly, in view of the frequency of accidents. The injury may be direct to the chest or indirect to the abdomen. Also it may or may not penetrate the chest wall. Penetrating instruments such as a knife or dagger may cause a tear in the heart muscle or aorta, with these there is usually blood in the pericardial sac around the heart.

Trauma and Valvular Disease Not infrequently the question arises whether a murmur in the heart, signifying a damaged valve, has not resulted from a strain or injury. I hardly believe that effort can produce changes in the valve even if it was previously diseased, but trauma of the heart may cause rupture of a valve. Yet this must be a very rare occurrence, indeed. This problem is almost always simplified by the

finding of enlargement of the heart and other murmurs presumably present for a long time, providing that the murmur in question was longstanding I saw such a case several years ago. A painter, H. G. No. 8979, 39 years old, claimed that he had been entirely well until six months previously when an iron gate weighing 200 pounds became unhinged and hit him in the lower back. He was forced to go home but returned the next day and continued at his regular employment during the next five months, when he found that work was too difficult for him. He was unable to carry a ladder or cans of paint and complained of shortness of breath. On examination I found two murmurs, indicating disease of both the aortic and mitral valves, and the size and configuration of the heart were those associated with a heart condition of many years' standing. This proved that the blow to the patient's back obviously played no role. Only when there is a definite history of injury to the heart and no evidence of previous heart disease may a murmur reasonably be attributed to the accident.

Commotio and Contusio Cordis A blow against the chest or abdomen may cause either of two conditions: there are functional derangement (commotio) and bruise (contusion) of the heart. In the former there are no actual anatomical changes in the heart, but, as in concussion of the brain, there is a physiological disturbance in the function of the heart resulting chiefly in irregularities in rhythm. In contusion of the heart the impact of the chest wall against the heart is more forceful, resulting in actual damage in the heart muscle, chiefly hemorrhages and lacerations. A favorite accident producing this condition occurs at the steering wheel with pressure against the chest. Such an accident may also rupture the heart and blood vessels. When the heart is bruised, heart failure with congestion of the lungs may set in acutely and result even in death. Occasionally the heart failure advances more gradually and is evidenced by swelling of the liver and legs.

Trauma and Coronary Occlusion In the literature trauma has sometimes been considered a competent cause of coronary occlusion or thrombosis. However, a detailed study of the subject² and the experience of my colleagues and myself have convinced us that trauma never precipitates classic coronary occlusion or thrombosis. The reported cases in which coronary occlusion was attributed to trauma prove on closer study to be actually instances of contusion of the heart muscle and not coronary occlusion. When the latter was present, its relation to trauma

was entirely coincidental Let me cite a case

H G No 7698, 46 years old, was feeling tired and out-of-sorts one day when he went to work While stacking coils one slipped out of his hand and struck the front of his chest Pain developed after a short time but he continued working for five days By that time the pain had become severe and he consulted a physician An electrocardiogram showed that he had sustained a recent coronary occlusion It was my opinion that the patient had long-standing disease of the coronary arteries and that the occlusion had been forming or had been completed prior to the trauma and actually may have led to the accident. This was indicated by the fact that the man did not feel well before coming to work Tiredness is a common premonitory symptom in coronary occlusion In any case, the injury did not produce the occlusion Cardiac damage may be caused by trauma, but it is due to contusion of the heart and not coronary occlusion The differentiation can usually be made with the electrocardiogram ²

When the heart is injured symptoms usually appear soon after the trauma has been sustained However, occasionally an attempt is made to link an accident to a heart attack many months later Thus, F S C, a man of 45, suffered a fracture of the skull from which he gradually recovered Eleven months after the accident he sustained a coronary occlusion which was attributed to the accident, in spite of the long interval and the fact that the man had long-standing heart disease with hypertension

Trauma and Angina Pectoris Due to Coronary Sclerosis What has been said of the relation of trauma to coronary occlusion holds to a great extent for angina pectoris due to coronary sclerosis Contusion of the heart may result in pain in the heart region soon after the accident, which may be repeated during a relatively short period But repeated attacks of pain or persistent angina pectoris over a period of months or years should not be attributed to injury to the heart except in the rarest cases Angina pectoris, as we pointed out earlier, is associated with disease of the coronary arteries, a process that takes years to develop In contusion the heart muscle, and usually not the coronary arteries, is injured and healing takes place after several weeks, with subsidence of symptoms The following case illustrates the problem J A No 6927, 46 years old, claimed that he was well until the truck that he was driving turned over and his left hand and arm were injured and his chest bruised

The laceration of his hand was sutured and he remained in the hospital eight days. Two or three weeks after the accident, he began to notice pain in the chest when he walked. This symptom persisted. Examination showed that he had had elevation of blood pressure and heart disease for some time. This was the basis of his heart pain, further proof of which is afforded by the relatively long period of two or three weeks which elapsed between the accident and the onset of the pain.

Trauma and Bacterial Endocarditis In rare instances trauma may produce an infection from which the germ may enter the blood stream and result in blood poisoning with infection of the heart valves, that is, an acute malignant endocarditis. This is the only type of endocarditis which is compensable. One common type of infection of the valves, subacute endocarditis, almost always takes place on valves previously diseased, either since birth or after rheumatic fever or syphilis. In most cases the infection is caused by a specific germ, the *Streptococcus viridans*. Although it is sometimes claimed that this disease may result from injury, there is no proof of this. Indeed, it is very unlikely since the *Streptococcus viridans* is practically ubiquitous. If an infection with this germ, resulting from trauma, could produce endocarditis the latter would be very common, whereas it occurs relatively infrequently. Furthermore, in hospital and private practice, a history of external abrasion or wound is never obtained in these cases.

Accidents Caused by Heart Disease In considering trauma one must not forget that a person with heart disease, no matter what the type, may sustain an accident as a result of temporary disability due to the disease. Unless one is careful the accident may erroneously be considered the cause of the heart condition. For example, a man, I. J. G., 60 years old, was driving his automobile and ran into a lamp post. Examination soon after revealed that he had suffered a heart attack. At first this was attributed to the accident. However, several witnesses stated that they had noticed the man slump in his seat prior to the accident. It was probable therefore, that the heart attack had occurred first and, as a result, he had lost control of the wheel. The heart attack was associated with long-standing heart disease.

Cardiac Irregularities Occasionally an irregularity of the heart rhythm may set in suddenly during heavy work or after unusual strain. The most common serious irregularity is termed *auricular fibrillation*. In this condition the rhythm is completely irregular. It may be transient

or permanent. Usually it is found in patients with heart disease but it may also occur when the heart is not affected organically. If it persists heart failure may ensue. While the irregularity usually sets in without any precipitating factor, it may follow an effort or injury in which case it is compensable even if the heart was abnormal. If the irregularity is transient the period of compensation should end with the cessation of the arrhythmia unless it has been severe enough to induce heart failure.

The following case illustrates the difficulty frequently encountered in determining the precipitating cause of auricular fibrillation. H. J., 33 years old, carried a box weighing 25 to 30 pounds from the street floor to the basement when he suddenly developed rapid irregular heart action. He had had five or six similar episodes previously. He smoked thirty cigarettes and drank three cups of coffee daily. Investigation showed that he was suffering from overaction of the thyroid gland, that is, hyperthyroidism or Graves' disease. Several possible causes of the heart irregularity were therefore present. Thus, Graves' disease is often associated with attacks of auricular fibrillation. The latter may also be precipitated by tobacco or coffee in susceptible persons. Finally, the exertion may have induced the attack.

These remarks about auricular fibrillation hold good for another disturbance in rhythm, namely, *paroxysmal tachycardia*. This is a sudden rapid, regular beating of the heart which may last a short time or several days. It is particularly apt to occur in people with normal hearts. *Skipped beats* or *premature beats* may appear following severe exertion or excitement, but they have very little significance. They are exceedingly common and probably occur occasionally in all of us, although most people are not aware of them.

Carbon Monoxide Poisoning In carbon monoxide poisoning the oxygen in the blood is replaced by the carbon monoxide and the tissues of the body are deprived of oxygen, a condition called anoxemia. As a result, damage is done to the blood vessels and tissues of the body. Although the brain is chiefly affected by the anoxemia the heart muscle may also be involved. If the patient survives the acute stage, this cardiac damage may become chronic and produce such symptoms as heart pain, shortness of breath and even heart failure. However, I am convinced that, as in the case of effort and trauma, carbon monoxide poisoning does not produce classical coronary occlusion or thrombosis. A number of writers have published cases purporting to show a causal relationship

between the two but the evidence has been very uncritical. Often the diagnosis of coronary occlusion has been made when actually merely heart damage is indicated. Most of the claimants were over the age of 45 and therefore probably had had diseased coronary arteries for some time. The following case report⁹ is a typical one in which coronary occlusion was attributed to carbon monoxide, but the improbability of any relationship will be obvious. A man, 36 years old, had lived near an oil and gas field and burned unrefined wet gas. He developed an illness characterized by temperature of 103° , stupor, delirium, cold sweat, nausea and vomiting. A diagnosis of coronary thrombosis was made, resulting from the chronic inhalation of carbon monoxide, even though no confirmatory laboratory tests were made. Even if the diagnosis of coronary occlusion is assumed to have been correct, its relation to the gas is purely speculative.

Before one attributes heart disease to carbon monoxide poisoning one should be certain that this has actually occurred and that heart disease had not been present previously. However, it must be remembered that carbon monoxide may aggravate a heart condition.

Effort Syndrome An interesting and important condition in compensation is effort syndrome or neurocirculatory asthenia or "soldier's heart." Originally described during our Civil War by Dr. DaCosta and studied in detail in the World War, it is also met in civilian life. It occurs in men more frequently than in women, and particularly in thin, asthenic persons in the young adult age group. It is a disturbance or weakness of the nervous control of the heart and circulation, and thus is a functional disorder, that is, there is no organic disease of the heart. In addition to numerous obviously nervous and stomach complaints, heart disease may be simulated by such symptoms as pain over the heart, palpitation and shortness of breath. The chest pain may be quite severe. Furthermore, there may be murmurs and changes in the electrocardiogram. The ability to exercise may be diminished. As a result, these patients often seem incapacitated. However, a careful history and examination usually distinguish this condition from true or organic heart disease. This disorder occurs in persons of constitutionally nervous tendency. These people may go along relatively well for long periods and then break down completely when faced with a specific situation or event. Acute symptoms may be precipitated by an emotional upset, whether it is an accident, a fright, or an unpleasant task, and it is some-

times difficult to exclude these factors as compensable. It is my impression that this disorder is only exceptionally compensable since these people are always on the brink of a precipice and symptoms are apt to appear at almost any time. In one case, E C, 21 years old, who complained of pain over the heart I discovered that sixty to eighty cigarettes were smoked daily and the pain may have been due to this. A careful history in these cases usually reveals adequate psychological cause for the patient's symptoms.

The Importance of an Accurate History At this point it will be obvious that in determining compensability following effort or trauma it is essential to obtain a very complete and accurate history. The latter should be taken in great detail and without any prejudice, and should include not only the events connected with the strain or accident but also the previous health of the patient and his subsequent course. In this way a number of facts may be elicited which are relevant to the case. For example, a longshoreman, J D No 9611, suffered a heart attack while working and was quite ill. Upon close questioning, it was discovered that a fellow longshoreman had noticed that he was very sick when he arrived that morning. His physician also told of previous heart disease. Hence, the attack may have occurred before the man went to work. Another case, G S No 6361, was a handy man of 44 who claimed that he had been entirely well until one day he picked up a 75 pound trap while working in a steam room, immediately following which he experienced severe pain in the chest which proved to be a coronary thrombosis. However, his family physician stated that the claimant had had high blood pressure for many years and pain for at least two weeks prior to the strain. Later on the claimant admitted that he had had high blood pressure. Another instructive instance was the case of a brewery truckman who carried numerous kegs of beer up several flights of stairs. As the history was first presented to me, the man was well until he died suddenly an hour later, presumably of coronary occlusion. However, I obtained a detailed history which disclosed the fact that the man had succumbed immediately after the exertion. Although we believe the latter did not precipitate the coronary occlusion, it cannot be denied that it may have contributed to the patient's death.

The history should be obtained in full as soon after the effort or trauma as the condition of the patient permits, and particular attention paid to any possible precipitating incident. I emphasize the importance

of an early history because I have frequently noted that patients brought to a hospital with coronary occlusion gave no history of strain or accident and yet, when the case came up in court at a later date, they testified that their symptoms had followed immediately or soon after some particular event. A comprehensive history elicited at the time of the injury or strain is more valuable than one taken later. This history, considered in the light of the preceding condition of the heart and the disability following the event, should enable one to make a correct and just evaluation of compensation.*

SUMMARY

The relation of effort, occupation and trauma to heart disease frequently offers a difficult problem and each case must be carefully considered.

Symptoms may be due to preexisting heart disease and the effort or trauma coincidental. Yet effort and trauma may aggravate previous heart disease. Effort does not damage a normal heart.

The effort is significant if it is unusual and not routine, and if symptoms arise immediately or soon after. The latter is also true of trauma.

A "stroke" may occur in the course of hypertension and arteriosclerosis. It is probably not related to effort, but the effect of trauma cannot be excluded.

Heart failure usually is a result of progressive heart disease and may be induced by infection. Only rarely is it precipitated by exertion, but the latter may aggravate it.

Angina pectoris is associated with coronary sclerosis. Individual attacks may be related to effort or trauma but later attacks or a persistent anginal syndrome rarely is.

Effort, occupation and trauma play no role in coronary occlusion. The opposite view is often based on a confusion of coronary occlusion with the syndrome of angina pectoris, coronary insufficiency with cardiac infarction, preliminary pain in coronary occlusion, and contusion of the heart.

Coronary insufficiency usually occurs in association with coronary sclerosis and may be related to effort and trauma.

Rheumatic fever rarely if ever is precipitated by effort or trauma.

Aortic aneurysm due to syphilis or sclerosis is not produced by effort.

* I wish to thank Drs. Harry L. Jaffe and Simon Dack for their help and criticism.

or trauma. In rare instances effort or trauma may lead to rupture or to dissecting aneurysm.

Trauma may produce commotio cordis and contusion of the heart. In addition, the heart, large vessels and, in very rare instances, a valve may be ruptured.

Trauma does not produce coronary occlusion and it probably does not lead to a persistent anginal syndrome.

Trauma may be the result, and not the cause, of heart disease.

Subacute bacterial endocarditis is not causally related to trauma with infection, but acute bacterial endocarditis sometimes is.

Cardiac irregularities may be induced by effort or trauma.

Carbon monoxide poisoning occasionally results in damage to the heart, or aggravates a preexisting condition, but it does not lead to coronary occlusion. Most cases of cardiac involvement attributed to carbon monoxide are based on insufficient evidence.

While neurocirculatory asthenia usually occurs in persons constitutionally susceptible to strain, in rare instances the onset of symptoms may be related to effort or trauma.

The problem of compensation in heart disease would be simplified considerably if a completely trustworthy history could be obtained in every case.

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HEPARIN AND THROMBOSIS

Harvey Lecture, November 28, 1940

C H BEST

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I WAS very pleased and, of course, highly honored when your President invited me to present to the Harvey Society the results of our work on heparin. In strenuous times like these there is a natural tendency to concentrate our attention on the application of physiological knowledge to the clinical problems of the moment. While I do not wish to infer that the members of our group have not been concerned with the many fundamental physiological and biochemical problems which have been encountered, the fact that heparin is of importance in certain aspects of military surgery has helped to sustain our interest in the subject during the past year.

I am honored this evening by the presence of Dr. Jay McLean, who in 1916 in Professor Howell's laboratory obtained evidence of the presence of the anticoagulant, heparin, in animal tissues. With heparin, as with many other compounds of biological importance, a careful search of the literature reveals the fact that several groups of workers had previously demonstrated the existence of a substance which was probably heparin (Schmidt,¹ Doyon,²) but the investigations of McLean³ were directly responsible for the further studies which have led up to the present situation. It is a privilege to pay tribute also to Professor Howell, who was responsible for so much of the original work on heparin and who anticipated the results of a great many of the relatively recent experiments. Professor Howell's interest and active participation in research on blood coagulation has extended over a period of more than fifty years. In his Harvey Lecture of 1917⁴ he describes the researches which led to the isolation of the anticoagulant and sets forth very clearly the important contribution which Dr. McLean made.

Before considering the role of heparin in the prevention of thrombosis I will spend a few minutes attempting to lay a foundation on which this story may be superimposed.

Thrombosis The term thrombosis is derived from the Greek word *θρομβος*. It was used by Hippocrates and Galen to describe a blood clot. A clot is, of course, a thrombus, but we distinguish this type from others by terming it a "red thrombus." A thrombus may be formed almost entirely by platelets, and this type is appropriately named a "white thrombus." While most thrombi are of the mixed variety—that is, with both red and white elements—emphasis will be laid this evening on the white thrombi since they almost invariably constitute the nucleus from which the red or mixed forms develop.

The early workers on thrombosis looked upon the process as an intravascular coagulation, and it is only within the last seventy years that the platelets have been recognized as cellular entities and their very special role in thrombosis appreciated. This change in our conception of the process is due to the work of Mantegazza,⁵ Hayem,⁶ Osler,⁷ Bizzozero⁸ and others. It is, however, in a very special measure, the findings of Bizzozero which demonstrated that under certain circumstances platelets may accumulate and thus constitute a nucleus for a thrombus. I regret that I will not have time this evening to discuss this work in detail, but this consideration would in any event only demonstrate the pathway by which one arrives at the conclusion that the factors governing platelet agglutination are as yet imperfectly understood.

COAGULATION AND PLATELET AGGLUTINATION

The differentiation of these processes was well initiated when Bizzozero observed the agglutination of platelets on the damaged intimal surface of blood vessels and it was advanced when Leo Loeb⁹ and others studied the phenomena in various forms of animal life. In certain arthropods, as many of you remember, fibrinogen is lacking and the agglutination process may, therefore, be readily studied uncomplicated by the phenomena of coagulation. In *Limulus polyphemus* the blood contains only one type of cell, the amoebocyte, and it is the agglutination of these which constitutes the protective mechanism against prolonged hemorrhage in these species. My colleague at McGill, Professor John Tait,¹⁰ found a somewhat similar situation in *Gammarus marinus* and noted that cell agglutination was the only obvious process in the formation of a clot. In some other species there are the so-called explosive corpuscles, the rupture of which promotes the formation of a coagulum. True blood coagulation as we see it in mammals is encountered first in certain ar-

thropods, the dekapods In some of these forms clotting occurs quite rapidly, but in others many hours are required (It is, I trust, not a sign of advancing years that during the last few weeks I have repeatedly thought of the charming existence one might lead in a secluded laboratory in the South Seas studying the development of these processes and the role of heparin in forms as far removed from man as possible It is difficult to reconcile these thoughts with those expressed in my opening paragraph The psychologists will undoubtedly suspect a conflict of emotions) It is apparent that the two processes, agglutination and coagulation, have been developed side by side during the evolution of the animal species Agglutination was the earlier of the two and this process persists in the higher forms It is primarily with this mechanism, and the effect of heparin on it, that we are concerned this evening It will be necessary to dismiss, with only the most fleeting reference, the whole fascinating question of the action of heparin on blood coagulation, our knowledge of which has been so rapidly advanced by the results recently obtained by Quick, Smith, Warner and Brinkhous, Ferguson and others It is now well established that heparin may act both as an antithrombin and as an antiprothrombin and that some as yet incompletely identified factor, or factors, present in blood serum is necessary for these actions

The interrelationship of the agglutination and clotting processes is a fascinating question and they undoubtedly are intimately associated under many conditions It can, however, readily be demonstrated in mammals that the two mechanisms are separable One has only to watch the clotting of blood from which the platelets have been removed, or the formation of a white thrombus in which no fibrin is detectable by the methods available, to conclude that there are at least no obvious indispensable relationships between the processes It remains possible, however, that further work will reveal that some process analogous to that of blood clotting plays a part in the agglutination of the platelets Many other theories which I will not even enumerate have, of course, been proposed, and it will certainly be necessary to understand this phenomenon much more clearly than we do at present before we can hope to decide by what means heparin affects it

HEPARIN

There is little doubt that the method of presentation of a scientific subject which makes the greatest appeal to a lecturer is to follow a trail

which he has helped to make. In availing myself of this privilege this evening I am adopting the suggestion which your President made in his invitation, but I wish to make it very clear that the members of our group have joined forces with the other workers in this field at a point separated from the origin of the trail by many years of hard and productive work. At this particular point, however, progress seemed to be very slow and the advance was undoubtedly hindered by two obstacles. A uniformly potent preparation of heparin which could safely be given in adequate quantities to experimental animals and to human subjects was not available, and convincing evidence that heparin inhibited platelet agglutination as well as coagulation had not been secured. While I will present the results of the Toronto work, which I initiated in 1929, in considerable detail I am anxious not to neglect the studies of Fischer in Copenhagen, of Jorpes, Bergstrom, Holmgren, Wilander and others in Stockholm, and of Chargaff and Olson and others in this country.

PREPARATION AND CHEMICAL PROPERTIES OF HEPARIN

For the past eleven years Dr. Arthur Charles, working first in the Department of Physiology and then in the Connaught Laboratories in Toronto, has been exploring the preparation and purification of the anticoagulant. Dr. Charles found that beef lung was the cheapest commercial source and this tissue has been used exclusively for many years for the preparation of heparin. When adequate amounts of crude heparin were available, attempts were made to isolate the active principle. In 1933 Charles and Scott¹¹ in Toronto and Schmitz and Fischer¹² in Copenhagen reported the isolation of a crystalline heparin. The Toronto workers obtained it as a sodium salt, the Danish workers as a brucine salt. Neither of these procedures lent themselves readily to large scale production. In 1936 Charles and Scott¹³ reported on the preparation of a crystalline barium salt (Fig. 1). This salt can be obtained in good yields and large amounts of heparin can be purified by this method. Heparin has been obtained as the crystalline barium salt from various other tissues of the ox and from other species. Jorpes,¹⁴ as a result of fractionation studies on impure beef heparin, has suggested that the crystalline anticoagulant is not a pure substance but a mixture of two closely related compounds which differ in their sulphate content and activity. Studies of crystalline barium salt do not support this view. In Table I

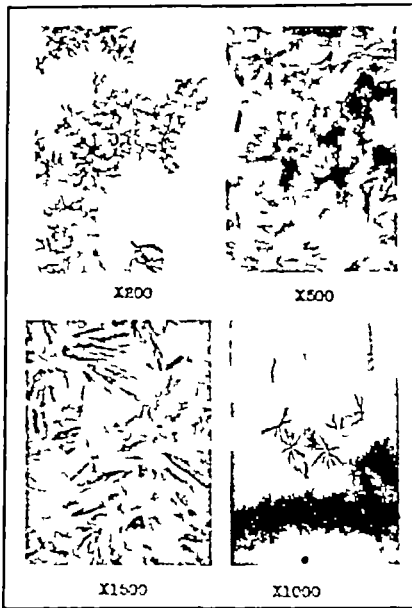


FIG 1 Crystalline barium salt of beef heparin (Charles and Scott) $\times 500$ and $\times 1500$ are magnifications of the same crystals as in $\times 200$

TABLE I

Starting material	Methods	Per cent Ash	Potency	Per cent N
			<i>u / mg</i>	
Beef lung	$\text{CdCl} - (\text{NH}_4) \text{CO}_3$	33.1	98	2.13
“ “	$\text{CdCl} - \text{Benzidine}$	33.8	98	2.04
“ “	Charcoal—Benzidine	33.7	104	1.89
“ “	Charcoal— $(\text{NH}_4)_2\text{CO}_3$	33.1	97	1.90
Beef liver	$\text{CdCl}_2 - (\text{NH}_4)_2\text{CO}_3$	33.8	100	2.20
“ “	$\text{CdCl} - \text{Benzidine}$	33.2	98	2.01
“ “	Charcoal— $(\text{NH}_4) \text{CO}_3$	33.3	98	1.90

some data obtained on beef heparin prepared from different tissues and by different methods are given. This is taken from a recent paper by Charles and Todd¹⁵. These samples were all prepared as the crystalline barium salt and in each case over 80 per cent of the activity present in the original crude heparin was obtained in the crystalline form. The ash and nitrogen contents and the potency of the heparin obtained from



FIG 2 Crystalline barium salt of beef heparin A With plane polarized light. B With crossed Nicol prisms

these various tissues by different methods are the same. These findings support the conclusion that the crystalline salt is a chemical individual. (Furthermore, it has seemed to the chemists in our group that Jorpes' own data scarcely bear out his contention that the activity of heparin is due to the sulphate-containing material in the preparation. In experiments designed to prove this point, he recovered 70 per cent of the sulphur and 50 per cent of the activity in his various fractions, while 30 per cent of the sulphur and 50 per cent of the activity were lost in the process.) The significance of the crystalline barium compound is the one point in which the results of our group, i.e., of Charles and Scott, differ from those of the Swedish workers. In most cases the findings of the two groups have been in accord. Some recent pictures of the crystalline heparin made by Dr Hamly, Department of Botany, University of Toronto, show the appearance of the crystals in plane polarized light and through crossed Nicol prisms (Fig 2).

A brief review of the chemistry of heparin establishes the following facts. Howell¹⁶ demonstrated that heparin is of a carbohydrate nature. Charles and Scott established the presence of nitrogen, and Jorpes the presence of sulphur in the form of a sulphuric acid residue. This latter finding led Jorpes to advance the theory that heparin is a chondroitin polysulphuric acid and this is the basis of all recent views on the chemi-

cal structure of heparin. Heparin differs markedly, however, from the chondroitin and mucosin sulphuric acid already isolated, both, of course, in its physiological action and in its elementary analysis (N : S ratio 2 : 5 instead of 1 : 1). Also Meyer¹⁷ has found that his enzyme which splits mucosin sulphuric acid has no effect on heparin. It follows, therefore, that conclusions regarding the nature of the carbohydrate portion of the molecule must be based on actual chemical studies of pure heparin and not on analogy between its structure and that of the known carbohydrate sulphuric acids. It was established by Jorpes and Bergstrom¹⁸ that heparin contains glucosamine and a uronic acid.

The recent investigation of Charles and Todd, working in Manchester, has thrown new light on the problem of the chemistry of heparin. On the basis of the analytical values which they obtained with the crystalline barium salt, they suggest the formula shown in Fig. 3. This

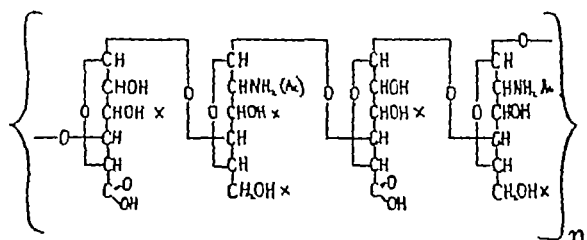


FIG. 3 Suggested basic structure of beef heparin (Charles and Todd)

is in conformity with the results of Reinert and Winterstein who have had no difficulty in preparing a crystalline heparin which has the same potency as the Toronto product. It is essentially the classical formula for mucosin sulphuric acid proposed by Levene which consists of two glucosamine and two uronic acid residues. Levene¹⁰ has suggested that this is polymerized by repeated glucosidic linkages to give a long chain structure similar to that of starch. Since there are five sulphate groups for each two amino groups, the basic unit of heparin presumably contains the four hexose groups. The five sulphate groups are probably disposed, Charles and Todd feel, as shown in the formula. The analytical data do not show clearly the degree of acetylation of the amino groups. The two carboxyl groups of the uronic acid molecules are either free or lactonized. The uronic acid is unknown. The crystalline salt is thought to be the barium salt of the sulphate groups rather than the carboxyl. Recently,

Jaques and Waters²⁰ in my laboratory have isolated the crystalline barium salt of heparin from dog liver by the same procedure as that applied to beef tissues. Dog heparin appears to be slightly different from that obtained from beef tissues. It has a higher potency and a lower sulphur content. Since its general chemical properties, i.e., solubility, crystalline form and so on, are the same as for beef heparin, there appears to be only a slight chemical difference between the two substances. Even more recently Jaques²¹ has prepared crystalline heparin from a number of species and I am indebted to him for the data in the following table (Table II). It is thus established that, while the heparin for any one species

TABLE II

Potency, Sulphur and Nitrogen Content of Heparins from Different Species
(Calculated for the free acid)

Species	Potency	Per cent sulphur	Per cent nitrogen
Dog	345	14.0	3.0
Beef	154	14.4	2.6
Pork	70	14.1	2.4
Sheep	32	14.7	2.8

All determinations were made on the crystalline barium salt (prepared by the procedure of Charles and Scott) and the corresponding values for the free acid were calculated by correcting for the water of crystallization, barium and ammonium-nitrogen present. The crystalline barium salt of beef heparin has a potency of 100 units per mg

is a chemical entity, a number of different heparins exist in the various species.

The groups in the heparin molecule responsible for its extremely high anticoagulant activity are, of course, of great interest. Both Howell and Fischer²² concluded that the uronic acid residues were responsible. Jorpes believes that it is the sulphate groups. A safer position, however, is that the anticoagulant activity is dependent upon all the groups in the molecule and their appropriate arrangement. The removal of *sulphates*, amino nitrogen or carboxyl groups causes almost complete disappearance of the anticoagulant activity. It can be shown that type substances containing any of these groups possess anticoagulant activity but none of these approaches the potency of heparin. The most potent substitute has

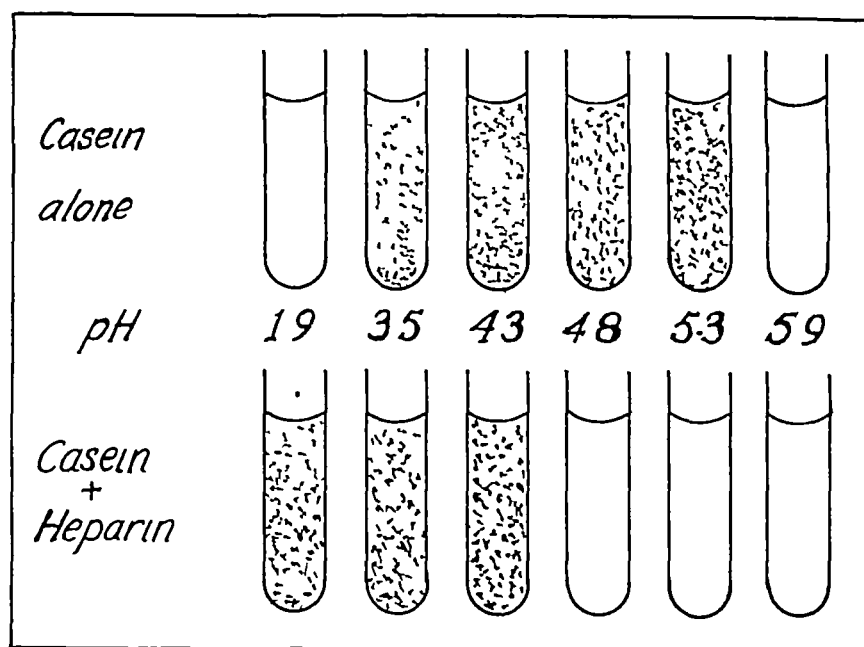


FIG 4 Effect of heparin on the isoelectric point of casein 10 mg casein and 1 mg heparin in each 100 cc of N/100 acetate buffer (Jaques)

perhaps one-tenth the activity of heparin and a much greater toxicity

The most significant biochemical property of heparin is its power to react with protein. This phenomenon was discovered and carefully investigated by Fischer²³. He concluded that heparin combines with proteins on the acid side of the isoelectric point. He demonstrated by suitable means that compounds could be formed with casein, hemoglobin, liver proteins and protamine. Fig 4, prepared for me by Mr Jaques, illustrates the reaction with casein. Casein is insoluble at its isoelectric point, pH 5, but the heparin-casein compound is soluble at this hydrogen ion concentration. The reaction of heparin with proteins may result in inactivation of the heparin if the protein used is able to compete with the clotting system for the heparin. Chargaff and Olson²⁴ have studied the reaction of heparin with protamine and have developed a simple test for heparin in blood and a means of neutralizing heparin both *in vivo* and *in vitro*. This reaction provides a rapid quantitative test for heparin in blood. These observations have been confirmed and somewhat extended by the members of our own group. The procedure has

been applied clinically by the Swedish workers for the neutralization of heparin, but we would recommend a very cautious approach to this use of protamine in clinical studies

THE STANDARDIZATION OF HEPARIN

At the present time there is a great deal of confusion in the literature due to the fact that there is no universally accepted unit of heparin. Reinert and Winterstein reported the results of comparisons between the various units. Without going into the details of these different units, one apparently represents the activity of about 1/100 mg of the crystalline barium salt of heparin, another one about 5/100 mg and a third 1/1250 mg. The Connaught Laboratories of the University of Toronto have donated 100 grams of the crystalline barium heparin to the Committee on Biological Standardization of the League of Nations, with the suggestion that the unit be set as the activity contained in 1/100 mg of this material.

TOXICITY OF HEPARIN

The fact that heparin forms stable salts with proteins with great ease is probably the explanation of the difficulty of removing protein substances completely from preparations of the anticoagulant. The explanation of the toxic effects of certain preparations of heparin may lie along this line. Howell and Mason relinquished their clinical trials because of toxic effects. The same problem was encountered in the first clinical trials in Toronto and in Stockholm. A high fever may be produced by impure preparations and gastrointestinal symptoms are common. When heparin is prepared from a crystalline barium salt the material is usually non-toxic but, on certain occasions, very objectionable reactions have been produced. Recently, through the work of Charles, Jaques and McHenry in Toronto, it has been possible to prepare products which are consistently free from these effects. Other groups may have had similar good fortune.

THE SITE OF FORMATION OF HEPARIN

As we have seen, heparin was first prepared from the liver, but Howell had also obtained small amounts from muscle, lymph nodes and blood. In 1933 Charles and Scott using their method which gave better

yields, isolated highly active heparin from lungs, spleen and kidneys. The lung was found to be particularly rich. More recently, Jaques and Charles have secured relatively large yields from intestinal mucosa. The physiological significance of the presence of such relatively high concentrations of heparin in the liver, lung and intestinal mucosa, is as yet unknown.

The histological and chemical contributions of Jorpes, Holmgren and Wilander²⁵ to our knowledge of (1) the source of heparin in the body and (2) the physiological function of the mast cells of Ehrlich deserves very special mention. The function of these cells has been debated since their discovery by Paul Ehrlich in 1877. The cells are characterized by the metachromatic staining of their granules by basic aniline dyes. They have a wide distribution but many investigators have stressed the fact that they are met with abundantly in connective tissue which is rich in blood vessels. It has been suggested that the mast cells are single-celled glandular organs of the connective tissue.

The granules of the mast cells are soluble in water (Ehrlich). Lison²⁶ found that high molecular sulphuric acid esters or polysaccharides produce the metachromatic staining (chondroitin sulphuric acid found in cartilage and elsewhere gives this color). Jorpes showed that heparin gave a similar reaction with toluidine blue and Bergstrom²⁷ noted the same color when the dye was mixed with synthetic sulphuric acid esters of carbohydrate. When toluidine blue was applied by Jorpes to various blood vessels, the characteristic staining was observed but proof that this was due to heparin was required (Fig. 5). Holmgren and Wilander, using this dye as a histological stain, found that the color appeared in the mast cells of Ehrlich which are found mainly in connective tissue near capillaries and in the walls of the larger blood vessels. The granules in the mast cells showed greater affinity for the dye than cells containing chondroitin sulphuric acid and the tint appeared to be somewhat different. Wilander,²⁸ using the method of Charles and Scott, found a very good correlation between the heparin content of various tissues and the number of mast cells. It thus appears that a new and fascinating chapter of histology and physiology is being written.

LIBERATION OF HEPARIN IN PEPTONE AND ANAPHYLACTIC SHOCK

The blood in peptone shock may be incoagulable (Schmidt-Mulheim and Albertoni, 1880) and many theories have been entertained in the

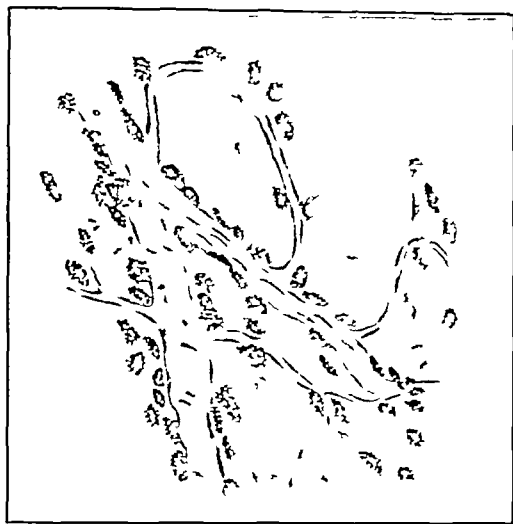


FIG 5 Mast cells stained through injection of a diluted solution of toluidine blue into the subcutaneous tissue of the rat. (Jorpes)

search for an explanation Howell²⁰ and Quick³⁰ have, however, obtained strong evidence in favor of the appearance of heparin during the shock. More recently, Jaques and Waters have neutralized with protamine the anticoagulant which appears in the blood, and Wilander has prepared highly active heparin from the blood of animals in peptone shock. Wilander has secured evidence that this anticoagulant comes, in part at least, from the mast cells in the liver (Figs 6 and 7).

In 1909 Biedl and Kraus³¹ found that the blood became incoagulable in anaphylactic shock. Since that time a great many investigators have studied the problem and almost every factor in the clotting process has been suspected. Quite recently Eagle, Johnston and Ravdin³² have obtained evidence that the antithrombin content of blood was greatly increased. They suspected heparin but did not prove its presence. Waters, Markowitz and Jaques³³ have shown that the clotting time of blood in anaphylactic shock can be reduced to normal value by the addition of protamine. Protamine neutralizes the effect of heparin by forming with it an inactive salt. Jaques and Waters have been able to isolate heparin in crystalline form from the blood of the shocked animals. The amount of heparin in the liver showed a marked fall (Fig 8).

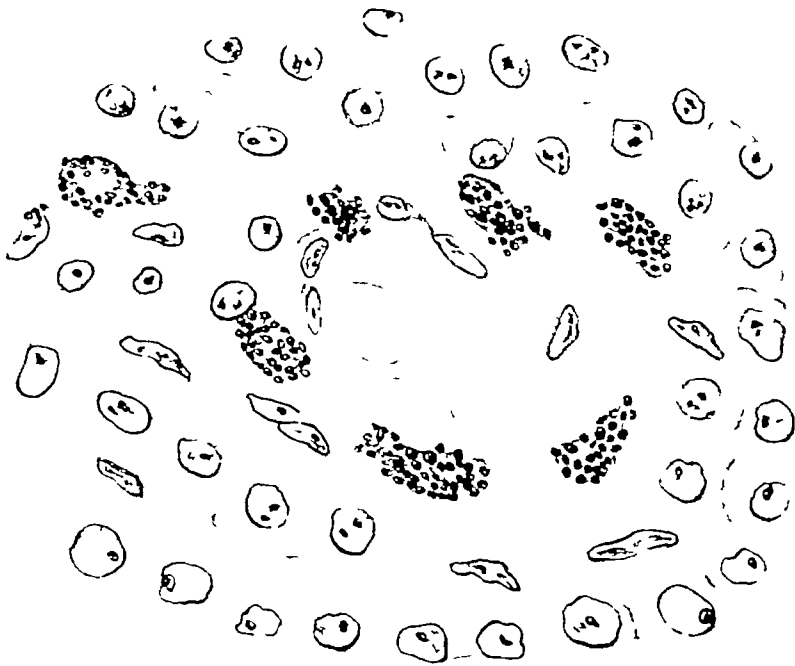


FIG 6 Mast cells in the liver of a normal dog The cells contain well fixed granules The mast cells are grouped around a small blood vessel (Wilander)



FIG 7 Mast cells in the liver of a dog after peptone shock The cells contain few granules which are small and for the most part faintly stained (Wilander)

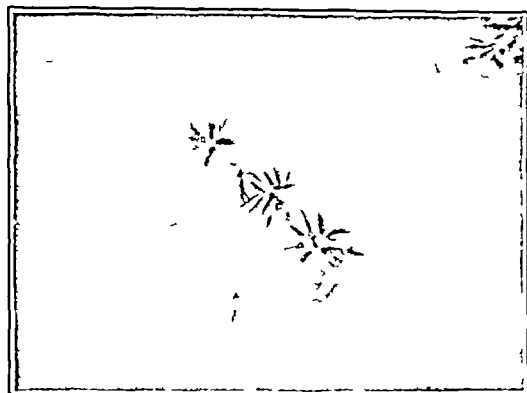


FIG 8 Crystalline barium salt of heparin isolated from blood of dog in anaphylactic shock, magnification $\times 450$ (Jaques and Waters)

EFFECT OF INJECTION OF HEPARIN

The effect of heparin *in vivo* is generally followed by the clotting time. The relationship between heparin concentration and dosage has been worked out for the dog by Jaques³⁴ and for humans by Crafoord³⁵. A logarithmic relationship is obtained, i.e., $\log T$ against \log dose equals a straight line. The effect of a given dose of heparin on the clotting time varies greatly from individual to individual. Crafoord has observed clinically that the curve changes in the same individual after operation, the heparin becomes less effective and he suggests that this may be a valuable clinical test to indicate a need for heparin. By such curves the heparin concentration present in the blood after injection can be calculated. Single injections of heparin, unless large enough to raise the clotting time to undesirable heights, have only a transient effect on the clotting time. Hence heparin is best administered as a continuous intravenous injection, and situations may arise in clinical practice in which the physician is well pleased that the clotting may be returned to normal limits very rapidly, simply by stopping the intravenous infusion.

After a lecture on heparin to a surgical group I was asked by one of the members if the subcutaneous administration of heparin was a safe procedure. I explained that we had reported the occurrence of subcutaneous hemorrhages in several animals of a large series and for this rea-

son the subcutaneous route, in human subjects, was not recommended. He apparently believed in testing the matter on his own patients because he then stated that he had frequently given subcutaneous injections of heparin and had encountered no difficulty.¹ The subcutaneous route may, however, advantageously be used in small animals, and we have experimented with substances which delay the absorption.

The relationship between the level of clotting time reached and the rate of injection appears to be quite constant amongst individuals. At present, this has only been established for the dog. In this way it is possible to maintain the heparin level in the blood and a constant raised clotting time by a continuous injection. It is usual to give a single injection when the administration is started in order to raise the clotting time to the new level. The actual clotting time for a given concentration of heparin varies with the individual.

Heparin disappears rapidly from the circulation. While some excretion of heparin occurs in the rabbit (Wilander), none occurs either in man (Reinert and Winterstein)³⁶ or in the dog (Jaques). Its rapid destruction may be due to an enzyme, heparinase, which Jaques,³⁷ working in my department, has recently discovered and described. The enzyme has a pH optimum between 5 and 6 but its exact physiological role is as yet quite unknown.

THE PHYSIOLOGICAL ROLE OF HEPARIN

Howell suggested that heparin was responsible for the fluidity of the blood. The low values for the heparin content of blood and high ones for tissues found by Charles and Scott led Mellanby³⁸ to suggest that heparin maintained the fluidity of the blood by being continually passed into it to neutralize the kinase from tissue breakdown. (Chargaff et al. have shown that heparin may appropriate the protein from the cephalin-protein complex which is kinase.) The position of the mast cells (in the vessel walls) also supports Mellanby's view. These findings suggest that heparin has a definite physiological role. There is little evidence, however, that heparin is a constituent of normal blood (Quick³⁹). The results obtained in attempts at isolation, the relationship between clotting time and heparin concentration, and the effect of protamine on the normal clotting time suggest that the heparin content of normal blood might be of the order of 1/10 unit per cc. At present, however, none of these methods is sensitive enough to detect heparin concentrations of this

order Therefore, no experimental evidence which is free of serious objections has been obtained At present the heparin concentration in normal blood and the physiological role of heparin must be considered an open question, but interesting developments in this field may be predicted

HEPARIN AND THROMBOSIS

It appeared to us that adequate proof would have to be provided that heparin prevented thrombosis, i e., platelet agglutination, before an extended clinical trial could be considered justifiable The results of experiments conducted by Shionoya suggested that heparin was not effective in preventing agglutination of platelets, but, as Professor Howell suggested at the time, there was a strong possibility that more highly purified heparin would exert an effect Gordon Murray of the Department of Surgery, with Jaques, Perrett and myself³⁹ found that thrombi forming on the intimal surface of veins which had been injured by mechanical or chemical means could be completely prevented by the adequate administration of purified heparin After three days of continual heparinization, the vein was completely healed and there was no indication that a thrombus would form subsequently at the site which had been injured In a later paper the formation of white thrombi was studied (Best, Cowan and MacLean⁴⁰) It was found that in dogs, cats and monkeys, the agglutination of platelets could be inhibited or prevented when large amounts of heparin were employed It may be remarked here that much higher concentrations of heparin were required to prevent agglutination of platelets in glass cells than in the body In the third series of investigations D Y Solandt and I⁴¹ produced coronary thrombosis by isolating the coronary artery and injecting sodium ricinoleate within the lumen This material was kept in contact with the intima for five minutes and the clamps on the vessel were then released In almost every case when no heparin was used a thrombus was present, and in the heparinized series this was a rare occurrence The fourth series, by Solandt, Nassim and myself⁴² had to do with the production of cardiac mural thrombi and the prevention of their formation by the administration of heparin A technique was evolved by which large mural thrombi could be regularly produced in the lumen of the left ventricle The endocardium of this cavity was injured by injecting sodium ricinoleate and the myocardium was damaged by ligating the an-

terior descending branch of the left coronary artery. The findings show that without heparin there was a rapid formation of thrombi, but none was seen in those experiments in which the heparin was given well before the injury was produced. These experimental results establish the fact that heparin is extremely effective in preventing platelet agglutination under a variety of experimental conditions. Solandt and I⁴³ have recently shown that with large doses of heparin the effect on platelet agglutination, unlike that on the clotting time which develops after a short latent period, may require from 15 to 50 minutes to become obvious under certain experimental conditions. This point should be kept in mind in experimental or clinical studies.

PHYSIOLOGICAL AND CLINICAL USES OF HEPARIN

The method developed by Charles and Scott is now used, in its entirety or in part, for the preparation and purification of all the highly potent heparin available on this continent or in Europe. The provision of an adequate supply of this material has made possible many new experimental and clinical investigations. To illustrate some of the newer physiological applications I may cite the investigations on exchange transfusions carried out in Toronto. The development of this method as we now use it was initiated by Dr. William Thalhimer and he collaborated with us in the first experiments which I will refer to in a moment. A good illustration of the usefulness of the exchange transfusion technique in highly heparinized animals is provided by recent experiments of Solandt, Nassim and Cowan.⁴⁴ The blood of a dog made hypertensive by the Goldblatt technique was exchanged at a rapid rate by means of a special pump (Solandt and Robinson)⁴⁵ with that of a nephrectomized donor. This procedure enabled these investigators to demonstrate for the first time the presence of a pressor substance in the systemic blood of a hypertensive animal (Fig. 9). The presence of this substance had, of course, been previously demonstrated by other workers in the blood from the renal vein. Solandt and I⁴⁶ have been using this technique to investigate the toxic theory of shock by exchanging the blood of a normal animal with that of one suffering from traumatic shock. The first of our series of experiments on exchange transfusions was, however, conducted with Thalhimer.⁴⁷ In these experiments we exchanged the blood of nephrectomized and normal dogs and noted the rapid lowering of the urea content of the blood of the uremic animal.

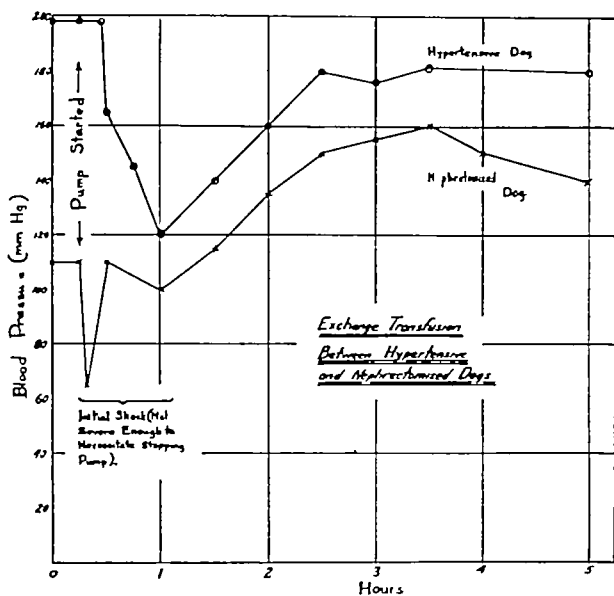


FIG 9 Exchange transfusion between hypertensive and nephrectomized dogs (Solandt, Nassim and Cowan)

and a great increase in the excretion of urea in the normal (Fig 10). In the report of this work we suggested that a clinical application might some day be made. We have been extremely interested to learn of the work of Duncan, Tocantins and Cuttle⁴⁸ (Fig 11), who exchanged the blood of uremic patients with that of normal subjects. They secured a very definite increase in the nitrogen excretion of the normal subject. In the two uremic patients which they studied in detail the authors suggested that there was a definite clinical improvement. These findings encourage the hope that some day the technique may be perfected by which the kidneys or perhaps some other organ of normal subjects may be made available, as it were, to patients in whom there is a serious *but presumably transient* deficiency in some physiological function.

A great many patients in Toronto, in Stockholm and elsewhere have been heparinized during the so-called danger period after operative procedures which have in the past been followed by a relatively high incidence of embolic phenomena. It is obviously extremely difficult to secure scientific proof of the influence of heparin under these conditions. The results have not, however, been unfavorable and in many

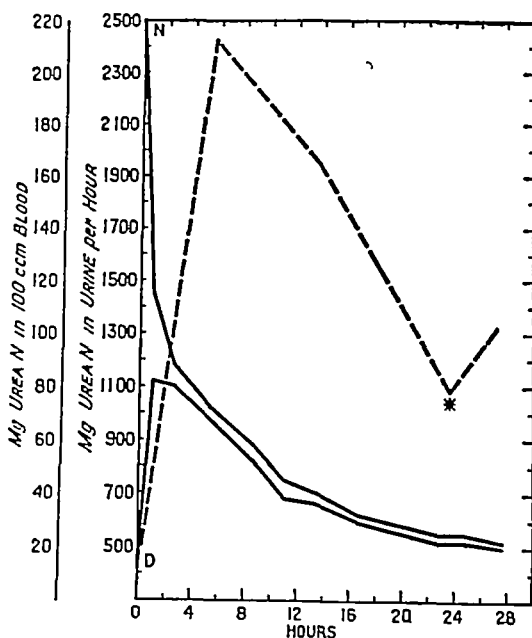


FIG 10 Exchange transfusion continued over full period. Continuous line = blood, interrupted line = urine, N = nephrectomized dog, D = normal dog, * = catheter plugged (Thalhimer, Solandt and Best.)

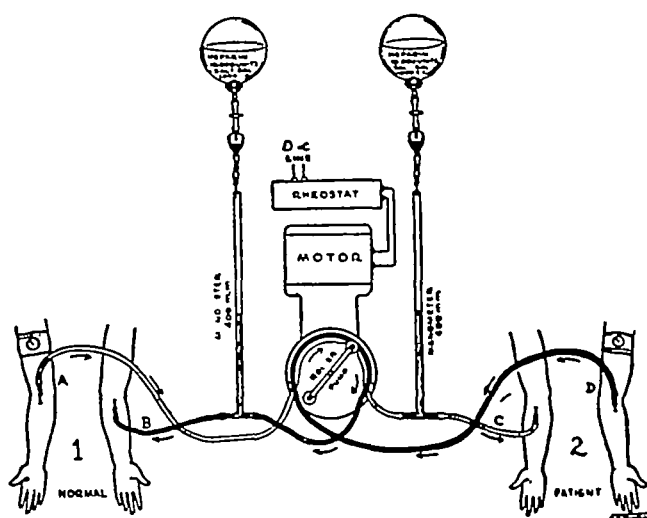


FIG 11 Diagram of the apparatus. 1A, delivering vein, 1B, receiving vein of the normal individual, 2D, delivering vein, 2C, receiving vein of the uremic patient. The 2 tubes rest exactly superimposed in a semi-circle around the periphery of the roller pump (Duncan, Tocantins and Cuttle)

individual cases the clinicians have been convinced that thrombus formation was prevented. We must always keep in mind the possibility that thrombi may be present before the heparinization is initiated. There is no evidence that heparin increases the likelihood that emboli will be broken off. Its action is to prevent the formation of thrombi and not to dissolve those already formed.

The results of Murray's work in Toronto, that of the surgical group in Stockholm, and of various surgeons in this country, leave no doubt that heparin is a valuable adjuvant in certain types of vascular surgery. Murray's work⁴⁹ on the substitution of veins for arteries in certain cases of arterial aneurysm, the removal of emboli which have severely damaged the intimal lining of blood vessels, and the repair of severed arteries, furnish dramatic examples of the advance in surgery which the purified anticoagulant has helped to make possible. Similar results have been obtained in various clinics in this country.

There seems to be little doubt from the results reported by Holman⁵⁰, Ploman⁵¹ and other Swedish workers that heparin is very useful in the treatment of thrombosis of the central vein of the retina. There will undoubtedly be an opportunity to test these conclusions in a large number of clinical cases.

In 1939 Kelson and White⁵² treated a number of cases of subacute bacterial endocarditis with sulphapyridine in combination with heparin. Kelson has continued this work and while he feels that favorable results, in some cases, have followed the use of heparin when the chemotherapeutic treatment was effective in lowering the temperature and sterilizing the blood, he also states that the value of heparin has not been conclusively established.

Heparin has been used in a few cases of coronary thrombosis in human beings, but not as yet in a scientific manner. It would appear that the only way to determine whether or not it is of value in this condition is to heparinize every other patient of a very large series. Judging from the experimental work (Solandt and Best) the incidence of mural thrombus formation and the extension of coronary thrombi, if this occurs, would be inhibited. If there were any other therapeutic agent available for the treatment of this condition, the use of a substance which demands such careful supervision as heparin, could not perhaps be justified. Since, however, it is the only material available which prevents the growth of thrombi, it would appear that the clinical cardiologist

might explore its possibilities in a carefully controlled series of observations. He will, of course, have no preconceived ideas with regard to its therapeutic value in the condition which he is studying, but he may start his investigations with the knowledge that, if given in adequate amounts, further thrombus formation will be prevented. He will also have to bear in mind that heparin, like many other effective weapons, is a "two-edged sword" and that its function is to prevent coagulation as well as to inhibit thrombus formation.

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DEATHS OF FELLOWS

FARLEY, OLIN EVERETT 140 East 54 Street, New York City, born in Lowell, Massachusetts, January 24, 1892, died in Harrison, New York, August 5, 1941, graduated in medicine from McGill University, Montreal, in 1915, elected a Fellow of the Academy April 5, 1934

Dr Farley was surgeon to the Manhattan Eye, Ear and Throat Hospital and consultant in ophthalmology to the Holy Name Hospital at Teaneck, New Jersey. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies

FRY, HENRY JACOB, Ph.D Westport, Connecticut, born in Lancaster County, Pennsylvania, May 2, 1892, died in Westport, Connecticut, August 17, 1941, received the degree of Doctor of Philosophy from Columbia University in 1925, elected an Associate Fellow of the Academy November 6, 1930

Dr Fry was professor of biology at the Washington Square College, New York

University, from 1930 to 1933, having been appointed as instructor in 1923. From 1931 to 1938, he was on the faculty of the New School for Medical Research

JOACHIM, HENRY 1111 Park Avenue, New York City, and 871 Park Place, Brooklyn, New York, born in Brooklyn, April 16, 1883, died in New York City, August 18, 1941, graduated in medicine from Cornell University Medical College in 1904, elected a Fellow of the Academy, November 2, 1922

Dr Joachim was associate physician on the staff of the Jewish Hospital, 1911-18, attending physician and clinical professor of medicine to the Long Island College Hospital, 1918-31, and head of the medical department at the Greenpoint Hospital, 1918-22. Since 1922, Dr Joachim was chief of the medical staff of the Israel Zion Hospital and Beth Moses Hospital, and since 1933 he was medical director of the Cumberland Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases. He was also consulting physician to the Sydenham Hospital

Dr Joachim was a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, a Fellow of the American Medical Association and a member of the County and State Medical Societies. He was a for-

mer president of the Kings County Medical Society and the Williamsburg and New Utrecht Medical Societies

KAST, LUDWIG 525 Park Avenue, New York City, born in Vienna, Austria, March 2, 1877, died in New York City, August 14, 1941, graduated in medicine from the Medical Faculty of the University of Prague, Austria, in 1903, received the degree of Sc.D. from Syracuse University in 1934, elected a Fellow of the Academy, April 7, 1910.

Dr Kast came to the United States in 1906, after postgraduate work in Vienna, Prague, Munich, London and Berlin, to continue his research in the physiology and pathology of digestion at the Rockefeller Institute.

In 1907, he was appointed instructor in medicine at the New York Post-Graduate Medical School and Hospital and was made assistant professor in 1909, and full professor in 1914. He became a member of the Board of Directors of the institution in 1912, and since 1914 had continued as an active Trustee of the school, specializing in teaching and research in problems of internal medicine and education. He also contributed to many medical publications on problems of experimental and clinical medicine.

In 1909, he was appointed secretary to the national committee of the United States of the International Committee on Post-graduate Medical Education, a position which he held until 1914 and in which he was largely instrumental in establishing many contacts with European medical universities for exchange of American teachers and students. His research in internal medicine and medical education soon made him widely known and in 1930 he became the President of the Josiah Macy Jr. Foundation for medical research.

Dr Kast was a Fellow of the American Medical Association, a member of the American Roentgen Ray Society, the American Gastroenterological Association, the Society for Experimental Biology and Medicine, the New York Pathological Society, the Harvey Society and the County and

State Medical Societies. He was a lieutenant-colonel in the United States Medical Officers Reserve Corps and in honor of his medical researches had been decorated by the Belgian Order of the Crown and the *Palme Academique* of the French Academy.

Dr Kast, who first proposed the establishment of the Graduate Fortnight of the Academy, which was instituted in 1928, continued to give inspiration to this enterprise until the time of his death. In honor of the founder of these Fortnights, the opening lecture of the Fortnight is designated the "Ludwig Kast Lecture."

NILES, HENRY D. 114 East 54 Street, New York City, born in Brooklyn, N. Y., November 18, 1901, died as the result of an automobile accident near Fort Peck, Montana, August 27, 1941, graduated from the Johns Hopkins University Medical School in 1925, elected a Fellow of the Academy, November 2, 1933.

Dr Niles was a member of the State and County Medical Societies, the American Academy of Dermatology and Syphilology, the American Dermatological and Metropolitan Dermatological Societies, and a member of the Alumni of New York Hospital. He was also Assistant Physician to the New York Hospital, Assistant Dermatologist and Syphilologist to the Post-Graduate Hospital, Dermatologist and Syphilologist to the Out-Patient Department of the Post-Graduate Hospital, Senior Dermatologist to the West Side Hospital and to the Out-Patient Department of the West Side Hospital.

SOUR, BERNARD 1124 Park Avenue, New York City, born in Shreveport, Louisiana, September 17, 1869, died in New York City, May 7, 1941, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893, elected a Fellow of the Academy February 6, 1902. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

STERN, ABRAHAM RICHARD Danbury, Connecticut, born in New York City, July 21, 1874,

died in New York City, May 8, 1941, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899, elected a Fellow of the Academy January 5, 1905. He was a member of the American Medical Association and the State and County Medical Societies.

STRONG, ARCHIBALD MCINTYRE 180 Ft Washington Avenue, New York City, born in Montclair, New Jersey, June 16, 1881, died in New York City, July 21, 1941, received the degree of A.B. from Princeton in 1904 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1908, elected a Fellow of the Academy January 6, 1938.

Dr Strong was associate physician to the Presbyterian Hospital, a Fellow of the American Medical Association, a member of the New York Society for Clinical Psychiatry and a member of the County and State Medical Societies.

WOODRUFF, WALTER STUART 421 Huguenot Street, New Rochelle, New York, born in Dunkirk, New York, April 10, 1883, died in Colebrook, Connecticut, August 19, 1941, graduate in medicine from the University of Michigan in 1906, elected a Fellow of the Academy January 6, 1927.

Dr Woodruff was attending surgeon to the Mount Vernon Hospital, 1910-1922, instructor in otolaryngology at the University

of Michigan, 1922-1925, attending otolaryngologist to the New Rochelle Hospital, 1925-1938, the time of his retirement, and consulting rhinologist to the Ossining Hospital, 1926-1931.

He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, a member of the American Academy of Ophthalmology and Otolaryngology, a former president of the Westchester County Medical Society, and a member of the Medical Society of the State of New York, and the New Rochelle Medical Society.

ZIEGLER, JEROME MARTIN 144 East 90 Street, New York City, born in New York City, June 23, 1894, died in New York City, August 25, 1941, graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1918, elected a Fellow of the Academy, April 7, 1927.

Dr Ziegler was a member of the State and County Medical Societies, a member of the American Medical Association and the Alumni of the Mount Sinai Hospital. He was Associate Surgeon to the Montefiore, Beth David, Sydenham and Riverside Hospitals, and Assistant Surgeon and Surgeon-in-Charge of the Urological Clinic at the Mount Sinai Hospital.

Since 1926 Dr Ziegler was a Police Department Surgeon in Queens County.

BULLETIN OF THE NEW YORK
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THE STEERING COMMITTEE AND ACADEMY FINANCING*

WHEN the Budget Committee of the Academy meets, the specter of a deficit will be absent for the first time in several years. This does not mean that the Committee can relax its vigilance, or even grant the various departments all the funds they request, but it does mean that the financial tension has temporarily eased and the Academy program for the ensuing year can be planned in orderly fashion.

For nearly a decade the Trustees have faced a financial dilemma. Confronting a tremendous increase in the demands on Academy services was the inescapable reality of steadily declining revenue from the capital funds. Income from sources such as dues and assessments of organizations having headquarters space within the building is virtually stationary and can not be expected to gain appreciably in any one year. The situation resolved itself into an annual reduction of the budgetary requests of the various departments even to the extent of crippling their activities.

Late in 1936 the Academy approached the new year with the prospect of having its 1937 budget off-balance in the sum of \$30,000. A fund-raising committee was formed which succeeded in raising \$23,216.50 that year among Fellows of the Academy and a few lay

Progress Report to the Academy Fellowship from the Committee Sept. 10, 1941

friends. With this money and by the exercise of rigorous economies the deficit was changed into a small favorable balance.

At the beginning of 1938 a deficit of \$33,000 was anticipated. Through strenuous efforts the Fund-Raising Committee succeeded in raising \$29,100.16.

As many of the 1937 and 1938 contributions were made with the stipulation that renewals could not be expected, the Trustees realized that the annually recurring financial problem was being met only temporarily. It was obviously time to take stock.

In May of 1939 the Council appointed a Steering Committee with Dr. Harold R. Mixsell as chairman to study Academy finances and make recommendations looking toward abolition of the hand-to-mouth existence. Associated with Dr. Mixsell were Doctors Shepard Krech, Robert L. Levy, Walter L. Niles, William Barclay Parsons and Charles F. Tenney, with the President and Director serving ex-officio. The Fund-Raising Committee, after completion of its task, was replaced by the Steering Committee and turned in \$10,047.50. At the close of 1939 the Academy had a substantial deficit. Then one of those things happened which you hear about but are slow to believe. In his annual address on January 4, 1940, President Malcolm Goodridge reviewed the Academy's financial picture including the announcement that the Academy was entering the new year with a deficit. The following day Mr. Bernard M. Baruch read an account of Dr. Goodridge's address in a New York newspaper and later dispatched his personal check for \$18,000 to cover the full amount, thus enabling the Academy to start the year with a clean slate.

After mature consideration the Steering Committee decided in 1940 to engage professional counsel in planning the Academy's finances. Under their guidance a lay council was formed as an auxiliary to the Steering Committee. Men prominent in the city's business and industrial life were invited to the Academy individually to meet with officers and members of the Steering Committee. Most of them knew little or nothing about the Academy, the services it renders the medical profession and the public, and its potentialities for greater usefulness. With only a few exceptions they enthusiastically agreed to serve. Therein the Committee learned a valuable lesson. They found that the Academy could have numerous influential friends outside the profession by carefully presenting its case and making known that lay support was welcome.

The Lay Council as originally organized consisted of Walter S Gifford, chairman, Arthur M Anderson, George Blumenthal, Lewis H Brown, Clinton H Crane, Marshall Field, Joseph M Hartfield, David M Heyman, Philip W Lennen, George W Merck, and Edward L Shea W Gibson Carey, Jr, has replaced George Blumenthal since deceased

Meantime the Steering Committee had been enlarged to include the following Fellows Doctors George Baehr, Henry W Cave, Arthur F Chace, John Stage Davis, James Alexander Miller, Alfred T Osgood and Carnes Weeks

Jointly the Steering Committee and the Lay Council worked out a plan to take care of the Academy's more pressing needs for the next five years This called for the raising of \$550,000 Of that sum \$250,000 or \$50,000 a year was to be set aside for budgetary purposes The balance or \$300,000 was to be spent for new stack floors and catalogue rooms of the library which for many years had been handicapped by inadequate space with stack floors filled to almost 100 per cent capacity

Naturally some dissension was heard "This isn't the time," "England needs all we can spare," "Don't build now," were a few of the comments But the Steering Committee, backed by the Council and Trustees, knew that there were only two choices either go ahead or sharply curtail Academy activities In the decision to go ahead they were supported by the Lay Council One internationally-known industrialist advised "We know what we have now, we don't know about the future"

It was decided to avoid the usual campaign machinery and also any direct appeal to the Fellowship as a whole It was felt that in the main the Fellows through their initiation fees, annual dues, and gifts during the campaign of the Fund-Raising Committee in the late 1930's had done about all that could reasonably be expected Instead interest was centered in philanthropically inclined citizens, smaller foundations known to be favorably disposed toward the advancement of medicine and certain commercial companies which have long profited from the Academy's existence Members of the Lay Council proved invaluable in providing contacts with these groups

The Steering Committee held 36 weekly meetings between October 1940 and September 15 of this year with an average attendance of 70 per cent The Lay Council was assembled only twice as a full body

these being dinner meetings, but there have been innumerable individual conferences between members of the Steering Committee and members of the Lay Council

Now the Steering Committee is happy to report to the Fellowship that the five-year plan appears reasonably certain of fulfillment. The Committee has raised in cash gifts or pledges \$181,519. It does not intend to stop work until the full amount is subscribed.

That is why Budget Committee members will have smoother brows when they take up their task this month. They have visual evidence that the combination of Steering Committee and Lay Council works, and are confident it will be 100 per cent successful.

Although it is pleasing to contemplate the prospect of balanced budgets during the stormy years ahead, the Trustees realize that this, too, may be only a longer stop-gap. For the last several administrations, presidents of the Academy have stressed the importance of increasing the endowment. Only this, it is believed, will place the institution on a sound basis.

In February, 1940, the Trustees charged the Steering Committee with the responsibility of placing the Academy on a sound financial basis. Under their leadership it is hoped to add \$1,000,000 to endowment, giving the Academy a total of \$4,000,000 in capital funds. As a matter of fact, a total of \$5,000,000 is needed for real security. Neither the Trustees nor the Steering Committee have any illusions about the magnitude of this responsibility. It is their sincere hope that all the Fellows of the Academy who prize their fellowship will assist in the undertaking. With such collaboration the \$5,000,000 ultimate goal can be reached within the next two years and the Academy put on firm financial footing before reaching its one-hundredth anniversary.

CARCINOMA OF THE STOMACH EMPHASIZING SOME OF THE MISCONCEPTIONS OF THE DISEASE*

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IN the evaluation of any disease one should try to determine if the disease is frequently encountered by the medical profession or is a disease only encountered in the large medical centers. For that reason carcinoma of the stomach should be emphasized as to its frequency in relation to carcinoma of other organs and as a cause of death as related to other diseases. The causes of death in the United States for 1938 as reported by the United States Bureau of the Census is given in Table I. From this report one sees that carcinoma is second only to heart disease as a cause of death. Now carcinoma of the stomach causes one-fifth of the deaths of carcinoma patients. Livingston and Pack¹ state that one-fourth to one-third of the deaths of carcinoma patients are due to stomach carcinoma. The error of their report is that they have included the liver and biliary tract carcinoma with the stomach cases. The Metropolitan Life Insurance Company reporting on carcinoma among their policy holders over a 25-year period, 1911-1935 inclusive, found that 32 per cent died from carcinoma of the stomach and liver. From 1917 they have separate records of carcinoma of the stomach, and the biliary tract. During this period 20.4 per cent died from carcinoma of the stomach and 8.7 per cent from carcinoma of the liver and biliary tract. Carcinoma of the female genital organs was second in importance and caused 20.1 per cent of carcinoma deaths. Carcinoma of the intestines, rectum, and anus was third and caused 13.6 per cent of the total carcinoma deaths. Carcinoma of the breast was fourth with 6.7 per cent.

One should consider what percentage of deaths of the total population are due to carcinoma of the stomach. The Metropolitan figures give 2.6 per cent when including the liver and biliary tract cases, and

TABLE I

ANALYSIS OF CAUSES OF DEATHS IN THE UNITED STATES IN 1938
(Source: Special Reports, United States Bureau of the Census)

	<i>Deaths</i>
Diseases of the heart	350,168
Cancer and other malignant tumors	149,214
Cerebral hemorrhage, cerebral embolism and thrombosis	111,567
Nephritis, acute and chronic	100,520
Accidental, other or undefined	93,805
Pneumonia, all forms	87,923
Tuberculosis, all forms	63,735
Diabetes mellitus	31,037
Arteriosclerosis (except coronary arteries)	21,208
Suicide	19,802

18 per cent when the stomach alone is considered. This latter figure is accurate by comparison with the figures from Bellevue Hospital. We found among 1,040,784 admissions 17 per cent were suffering from carcinoma of the stomach. The Metropolitan figures cover all ages, and our figures, all admissions including pediatrics, obstetrics, psychiatry and neurology.

WHAT DOES THE FUTURE OFFER TO ONE SUFFERING FROM CARCINOMA OF THE STOMACH?

Livingston and Pack¹ in their most comprehensive review have reported 14,475 cases of gastric carcinoma from the world literature with 2,861 resections of the stomach, or a resectability of 18.7 per cent. From these figures one would be very favorably impressed as to the chance of removal of the growth, which is approximately 1 in 5. Before accepting this as being the real percentage one must remember that their report includes the large medical centers of the world and in no way includes the patients in private practice who never enter a hospital or clinic, nor does it include the small hospitals of the country. For that reason we undertook to review the cases of carcinoma of the stomach admitted to the Fourth Division at Bellevue Hospital for a 20 year period, and we have reported on these findings.² It was our feeling that

TABLE II

BELLEVUE SERIES
Relation of Operability to Duration of Symptoms

Duration	Number	Non-operable	Operable	Resection*
Less than 1 month	62	41	21	3
1-3 months	82	65	17	5
3-6 months	82	57	25	5
6-12 months	70	45	25	5
1-2 years	65	43	22	3
2-3 years	19	15	4	1
3-5 years	15	10	5	1
5-10 years	15	12	3	1
Over 10 years	4	2	2	
Unknown	30	6	24	
Total	444	296	148	24

The figures in this column are included under operable

the ward service of a large municipal hospital would more nearly represent the true picture of the disease for the country than reports from clinic and medical centers which received referred cases. The cases entering large medical centers, having been selected by the family physician, would give a false sense of optimism for the disease. In studying 444 carcinomas of the stomach we found two-thirds, or 296, inoperable on admission. Of the 148 operable cases only 24 were resectable or 54 per cent of the total admissions.

The point that is always stressed in discussing carcinoma of the stomach is the importance of making an early diagnosis. It is worth emphasizing some of the reasons why an early diagnosis is not made. In our Bellevue study we were amazed at one finding, namely, the patient with symptoms of one month's duration has no better chance of removal of the growth than one with symptoms of one year's duration. These findings are illustrated in Table II. It occurred to us that cases from another hospital would not confirm this observation. Therefore the ward cases admitted to Post-Graduate Hospital for the past 20 years have been reviewed and are being reported. We excluded any ward

TABLE III
POST-GRADUATE SERIES
Relation of Operability to Duration of Symptoms

Duration	Number	Non-operable	Operable	Resection
Less than 1 month	11	4	5	2
1-3 months	33	4	22	7
3-6 months	48	17	24	7
6-12 months	48	11	25	12
1-2 years	24	5	9	10
2-3 years	12	2	5	5
3-5 years	6	1	2	3
5-10 years	5		4	1
Over 10 years	3		1	2
Unknown	6	1	4	1
Total	196	45	101	50

case admitted from an Attending Physician's office and accepted only the service cases. There were 196 cases and Table III gives the findings for the group. The percentage of resections for the total group was 25.5 per cent, but of forty-four patients with symptoms of not over 3 months' duration only nine were resectable, which is only 20.4 per cent resectability.

WHY IS IT DIFFICULT TO DIAGNOSE CARCINOMA OF THE STOMACH EARLY WHEN WE HAVE SO MANY REFINEMENTS IN DIAGNOSTIC METHODS?

It is difficult for the pathologist to diagnose carcinoma of the stomach from an ulcer of the stomach. There are two schools of thought on the point as to whether a gastric ulcer becomes malignant. During the past three decades the percentage has ranged from 70 per cent for some pathologists to 1 per cent for others. This fundamental point is very important as the advice given a patient with a gastric ulcer hinges on this basic concept of the disease.

If a high percentage of gastric ulcers develop malignant degeneration, then immediate operation should be recommended with the risks

attended by such a procedure Schindler⁴ in a very recent article has discussed this point and, to quote

"For a long time the opinion was prevalent that many gastric carcinomas develop on the soil of benign ulcers" This opinion, however, is now almost untenable Walter Lincoln Palmer contends "that the existence of carcinomatous degeneration in benign ulcer remains to be proved conclusively Gastroenterologists who carefully watch their ulcer patients over a period of several decades have never seen such an ulcer develop into a carcinoma Peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer Indeed, there is evidence that the carcinoma may be completely digested away by peptic activity, leaving a typical benign ulcer Probably a carcinomatous ulcer is malignant from the beginning"

In the stomach clinic of the Fourth Division at Bellevue Hospital we have taken the same stand and now have had 13 years of experience without cause for regret In 1937 we published⁵ our results on gastric ulcer and gastric carcinoma We wish to emphasize at this time that, if there is the slightest doubt in the differential diagnosis of a gastric ulcer from gastric carcinoma, the patient should be advised to have an immediate operation so as to eliminate this possible error This debatable point will never be settled until a central bureau for registering all five-year cures of carcinoma of the stomach has been established, in that way eliminating any skepticism of the five-year cures being due to inflammatory lesions instead of a true neoplasm The following case will illustrate the state of confusion as to classification by competent pathologists

A male, 38 years of age, was seen March 1939 complaining of vague stomach symptoms and vomiting X-rays of the gastrointestinal tract were negative in July of 1938 In January 1939 they were repeated at the same hospital and found to reveal a deformity of the pylorus which was considered carcinoma A re-check of the x-rays at Post-Graduate Hospital confirmed the findings of carcinoma of the pyloric end of the stomach At operation on March 11, 1939 a lesion was found on the lesser curvature 1 inch from the duodenum, and clinically it was impossible to state whether the lesion was an ulcer or carcinoma, but a subtotal resection was done and some lymph glands were encountered in the gastrohepatic omentum around the pylorus The sections of lymph glands were negative for a metastatic carcinoma To quote the pathological findings

"The question of malignancy in this case is rather difficult to decide, because the changes are not clear cut. It was my opinion at first that the changes in the glands could be interpreted as atypical regeneration of epithelium in a healing ulcer. However, the slides were shown to several other pathologists, whose opinions are given below."

Three are inclined to regard the lesion as not malignant. One has seen similar glands in a case of syphilitic ulcer of the stomach.

Three regarded the lesion as malignant. One calls attention to the superficial nature of the ulcer, and thinks that only a malignant condition would cause this and lead to symptoms warranting operation. He feels that the lesion was malignant from the beginning and he is pessimistic as to the outcome.

Two consider the malignancy as an early one, and give more favorable prognosis.

Final diagnosis "In view of the above opinions, it is better to consider this case as one of carcinoma of the stomach."

Schindler¹ has given Borrmann's macroscopic classification of gastric carcinoma, which should be of aid to the surgeon, and he describes four types of growth. Schindler, following Borrmann, divides them as follows:

"The first gross type of gastric carcinoma is the polypoid carcinoma. This is a sharply limited growth often looking like a mushroom with overhanging edge, its surface presenting numerous nodes and nodules which usually are of different sizes. Only at a very late stage will ulceration of this surface develop. The mucosa surrounding this type of tumor is often thoroughly atrophic. This type is not a frequent one. According to my own statistics it is found in 2.9 per cent of all gastric carcinomas, if carcinoma of the cardia is omitted. In my experience this type grows slowly and, it seems, never changes into another type, but remains polypoid and sharply limited. Microscopically most tumors of this group are well differentiated adenocarcinoma, and it seems that here radical operation at not too late a stage gives very good prognosis.

"Type 2 is a very important form. It is found rather infrequently, namely 17.6 per cent of all cases. It is an ulcer surrounded by an elevated wall. This wall has a steep slope toward the surrounding mucosa and is sharply demarcated all around against the surrounding mucosa. The floor sometimes shows necrotic material of all colors—brown, purple, gray, dark red or white. Sometimes necrotic, gray white crystal-

like excrescences can be seen floating in the current of air introduced during examination. The wall may be smooth or, more frequently, is nodular and contains shallow erosions. Its dark red color, then, is in marked contrast to the pale color of the surrounding mucosa. Since the surgeon tries to operate as soon as possible on these tumors he rarely has the opportunity to watch gastroscopically their course over a long period of time, but sometimes the patient may refuse the immediate operation and then such an observation may become possible. Within one week the thickness of the wall may double. However, I have never seen this sharply limited wall become diffusely infiltrative at a later stage. The number of such observations is naturally still too small to permit the definite statement that such a transition is never possible. The observation, nevertheless, is an amazing one because the microscopic structure of these carcinomas is not a uniform one. They often show little differentiation and look rather malignant microscopically.

"The startling point about these type 2 carcinomas is that metastases develop at a relatively late stage and often lead to an extremely satisfactory end result, to cures of long duration if an operation can be performed at not too late a moment, whatever their microscopic structure may be. These are the well-known tumors which may reach the size of a fist, which can well be palpated through the abdominal wall and which are definitely movable. This is the form of carcinoma which at x-ray examination frequently gives the so-called meniscus sign of Carman.

"In the type 3 carcinoma of Borrmann an ulceration is found also. This ulceration has a wall, but the wall is found only at one side of the ulcer and does not slope as steeply as does the wall of the type 2 carcinoma. There is a more gradual transition, and the ulcer itself, although sharply limited at one side, blends diffusely at the other side, and there, diffuse and progressive infiltration of the neighboring mucosa is seen. This type 3 carcinoma occurs in 16.3 per cent of all cases. Here again the microscopic pictures are not typical at all.

"The type 4 of Borrmann is the diffuse infiltrating type, which unfortunately occurs in 63.2 per cent of the cases. No sharp limit will be found anywhere toward the normal gastric mucosa either with the eye or by palpation, sometimes the entire stomach may be infiltrated. In this case, in which the stiff nodular infiltration is seen, the entire

stomach was found gastroscopically to be involved at the very first observation, almost two years before the patient died. Within this infiltration, ulceration may develop—shallow ulcers or deep ones. They never show the sharp edge of the typical benign ulcer. These type 4 carcinomas seem to be not very favorable tumors. I have never seen a complete cure after the resection of such a tumor, but naturally the material is too limited to permit any definite conclusions.”

With the divergent views on carcinoma of the stomach the natural question arises as to how the diagnosis can be made. In our reviews from Bellevue Hospital and Post-Graduate Hospital we found the following symptoms as listed in Tables IV and V.

The first diagnostic procedure is a gastrointestinal x-ray series. This properly done will diagnose 95 per cent of the carcinomas of the stomach. One must remember that a very early carcinoma may not be discovered and a few weeks later, due to its rapid growth, the diagnosis is easily made. This type of case offers a hopeless prognosis even if an early diagnosis is made.

The gastroscope is now of indispensable service in establishing the diagnosis of carcinoma of the stomach. A word of warning is that the gastroscopist must have had considerable experience to be of real value in these cases. If the gastrointestinal x-ray series is negative and the age or symptomatology suggests carcinoma of the stomach, a gastroscopy should always be performed.

Gastric analysis. This procedure should not be overlooked and in cases with stomach symptoms presenting a low free hydrochloric acid, a gastrointestinal x-ray series should be ordered. If the x-ray examination is negative and the symptoms persist with a low free hydrochloric acid finding a second gastrointestinal x-ray series should be ordered after a few weeks. In from 15 to 20 per cent of carcinomas of the stomach the free hydrochloric acid will be in normal limits, which should be remembered in the differential diagnosis between an ulcer and carcinoma of the stomach. The presence of blood in the gastric analysis is of importance, as between 50 and 65 per cent of the carcinomas of the stomach have blood, while the incidence of blood in ulcer of the stomach is lower, which is explainable in the size of the two lesions.

The determination of the cholesterol content of the urine is another laboratory procedure worth considering. Bruger⁶ has found that patients

TABLE IV
BELLEVUE SERIES
Presenting Symptoms in Order of Frequency

Symptom	Number	Percentage
Pain	412	92.8
Loss of weight	398	89.6
Weakness	269	60.5
Cachexia	195	43.7
Jaundice	103	23.2
Nausea or vomiting	73	16.3
Hematemesis	41	9.2

TABLE V
POST-GRADUATE SERIES
Presenting Symptoms in Order of Frequency

Symptom	Number	Percentage
Pain	154	76.2
Loss of weight	145	71.8
Nausea or vomiting	121	59.9
Anorexia	64	31.7
Weakness	55	27.2
Cachexia	45	22.3
Jaundice	7	3.5
Hematemesis	7	3.5

with carcinoma of the gastrointestinal tract may eliminate in the urine as high as 40 mg of cholesterol in 24 hours, while a normal person does not eliminate over 2 mg in 24 hours. The amount of cholesterol eliminated is highest in the early stages of the disease.

THE SURGICAL MORTALITY AND FOLLOW-UP OF CARCINOMA OF THE STOMACH

Livingston and Pick¹ in reporting on the mortality since 1920, re-

port 3,127 cases of gastric resection with a 22 per cent mortality. These figures are from the large clinics and represent the most favorable picture. The follow-up as given by them for 3-year cures is 29 per cent, 5-year cures, 19 per cent, 10-year cures, 10 per cent. These figures are largely based on the cases traced, which is always misleading and gives a much higher percentage of cures because the dead cannot reply and the relatives are not interested in replying to follow-ups. Then of 100 carcinomas of the stomach receiving the best surgical treatment in the large clinics, 18.7 per cent can be resected and of those that are resectable there will be a 22 per cent mortality. Of the patients leaving the hospital 19 per cent are alive after 5 years, which means in 100 cases of carcinoma of the stomach only 2.8 per cent will survive 5 years after the best surgical care.

There is nothing that offers a cure except radical surgery, but the future of this important disease does not lie in the repetition of early diagnosis and radical surgery, because very little has been accomplished in the past two decades from this teaching, if the questionable gastric ulcers are eliminated from the follow-up reports. One fact about carcinoma of the stomach is that it attacks men in the ratio 3 to 1 as compared to women.

CARCINOGENESIS AS IT RELATES TO CARCINOMA OF THE STOMACH

In a recent report² of statistical and diagnostic data on cases of carcinoma of the stomach, their discouraging status was emphasized. The magnitude and seriousness of this problem is realized when one is confronted with a condition that accounts for one-fifth of the total carcinomatous deaths annually. That has led us to review the experimental work on carcinogenesis with the hope it might throw some light on this serious problem. For complete details on this review you are referred to the original article of Abrahamson and Hinton.⁷

Over 88 per cent of the cases of carcinoma of the stomach fall between the ages of 35 to 70 with the peak of incidence occurring in males between 50 and 55, and females between 55 and 60. The age incidence and sex discrepancy in gastric carcinoma are two facts which stand out in almost every large series reported in recent years. Balfour and Hargis,⁸ Smithies,⁹ Friedenwald,¹⁰ Masson,¹¹ Minnes and Geschickter.¹²

Many authors, largely physiologists and experimental workers, have

definitely proved the production of malignant growths in animals, by the injection and application of estrogenic substances. The carcinogenic effect of estrogenic hormones on tumor formations, have been shown to be both actual and definite by repeated experiments. Flacks and Ber,¹³ after producing cutaneous tumors in mice by the action of methyl-cholanthrene, found that the percentage of tumors was less when they were previously injected with testosterone propionate.

The close relationship between the chemical structure and biological properties of many highly carcinogenic substances and that of the estrogenic and androgenic hormones, has recently been demonstrated. The highly carcinogenic activity of hydrocarbons, such as methylcholanthrene and its derivatives, have been confirmed in several laboratories. It has been shown that certain estrogens and other normally found substances, via their sterol radicals, can be demonstrated to have an "inherent tendency" to pass into such high carcinogenic substances as methylcholanthrene and its derivatives (Rossner,¹⁴ Barry, Cook et al,¹⁵ Shear,¹⁶ Cook and Dodds,¹⁷ Flacks and Ber¹³). These findings have been well summarized in recent reviews by Cook¹⁸ and Needham.¹⁹

Experimental work with the injection of carcinogenic agents into various tissues, has shown that tumors develop more readily in some than others. A species difference has also been noted. Certain cells within the organism are more susceptible to neoplastic transformation than others under equal contact with carcinogenic agents. However, it has also been noted that the response of a given tissue to a carcinogenic agent is specific for both cell and type of carcinogenic agent, and has no relationship to spontaneous tumor formation. Rusch, Baumann and Maisson²⁰ injected the submucosal layers of the stomach of rats with benzopyrene in three cases and caused the formation of myoma spindle cell sarcoma and adenocarcinoma of the stomach. Similar injection of the duodenum did not cause tumor formation.

Stewart,²¹ although causing the formation of gastric adenocarcinoma in four mice by the injection of methylcholanthrene into the muscular tissues of the stomach wall, believed that the gastric mucosa is relatively resistant to the action of methylcholanthrene. In this connection, the work of Perry and Ginzton²² has importance in that they seem to have broken down the resistance of the mouse stomach to malignancy by combining 1, 2, 5, 6, dibenzanthracene with theelin thereby causing

gastric malignancies which were not caused by the use of 1, 2, 5, 6 dibenzanthracene alone

Studies on sterols present in the human blood stream show that several are related to highly carcinogenic substances, not only by chemical formulae and physiological action, but by biophysical and biochemical reactions. They are in themselves carcinogenic in experimental animals, although under ordinary circumstances in the human body, they do not bring about this change.

The inherent tendency however, of some of these sterols to change into carcinogenic substances under chemical physiological circumstances not foreign to human metabolic processes, sheds light on their potentialities (Needham,¹⁰ Cook and Kennaway,²¹ Fieser²⁴)

It is well known that during that period of life when carcinoma most frequently occurs, there are radical changes in the content and nature of the hormones, specifically the gonadotropic, estrogenic and androgenic hormones, as evidenced by chemical recovery from the organs, blood and urine, and by the involutionary and regressive changes which take place during this period. Estrogenic and androgenic substances have been shown to influence the incidence of carcinoma in experimental animals. It has also been reported that very slight alterations in the chemical structure of estrogenic and androgenic hormones in their proportional relationship to each other, may transform them into active carcinogenic agents (Korenchevsky and Hall²⁵)

Since it is our contention that the gastric mucosa acts as a gland of both internal and external secretion, its activities, therefore, are subject to regulation by endocrines produced by glands elsewhere in the body. Since interchange and interactivity of the glands of internal secretion have been demonstrated, it is logical to assume that the activities and secretion of the gastric mucosa should be added to the roster of glands whose functions are interdependent and subject to the carcinogenic effects of other hormones.

Peculiarly, estrogen of all the hormones, has been proved to have carcinogenic activity. It has been shown that in certain instances, androgens are able to retard or prevent the experimental induction of tumor development (Nathanson and Andervont²⁶). On the basis of these and similar extensive experimental work on rabbits, and by means of a theoretical chemical study, Murlin et al²⁷ have concluded that estrogens owe their carcinogenic activity to their necessity for oxida-

tion Prevention of this action is accomplished by androgens which provide hydrogen acceptors—thus titrating the hydrogen which estrogens have to spare and preventing the derangement of normal cell life In these experiments, with the exception of testosterone propionate, the effective materials used in the protection against tumor formation and prevention of metastases were urinary extracts and it is quite possible that other unidentified sterols and their related products were present

Although there can be no question of the carcinogenic activity of estrogens in lower animals, it is certain that the formation, activity and metabolism of hormones vary in different species These differences have been observed between rats, mice and rabbits and it is very likely that the metabolic processes affecting hormone activity in the human body differ materially from those in animals in which tumor growth was retarded by androgen injection Although it is well-known that malignant tumors are common in elderly dogs, carcinoma of the stomach is a rarity (Feldman²⁸) In 142,000 necropsies in mice, only fifteen spontaneous tumors of the stomach were found Wells et al²⁹ have emphasized the striking infrequency of alimentary tract cancer in animals, with the exception of man where over one-half are found in the alimentary canal

We believe our own statistical and clinical findings agree with animal experiments to indicate that sex hormones affect the incidence of tumor formation Controversial findings by competent workers are reported, in that both estrogens and androgens have been shown to have protective powers against tumors Estrogens have been reported both as a carcinogenic substance and as an immunizing agent against tumor inoculation and metastasis It would seem that the disproportion between these two hormones and other hormones is of greater importance than the activity of either one However, since it has been determined that hormone effects are the resultant of the algebraic sum of all the endocrine secretions, we believe that several other hormone effects are involved, viz pituitary, thyroid, corpus luteum and adrenal hormones The tumor forming and the tumor protecting effects of androgens and estrogens are not specific direct effects but general and indirect

We realize that the experimental work mentioned is incomplete, however, the problem of gastric carcinoma is of such tremendous pro-

portions and importance, that we believe many experimental and clinical observations by various workers with sufficient material will be necessary to bring us a correct evaluation of the data referred to, and its true relationship to carcinoma of the stomach

CONCLUSIONS

- 1 From personal observation during the past 13 years in the Stomach Clinic of the Fourth Division at Bellevue Hospital where we observed over 1200 ulcers of the stomach and duodenum, it is our feeling that an ulcer rarely if ever becomes a carcinoma of the stomach
- 2 In a previous report on the gastric ulcers from our clinic numbering 104 cases we found nine in which a differential diagnosis between ulcer and carcinoma was not possible
- 3 Of these nine cases, all were advised immediate operation and eight submitted. Of the eight cases six or 75 per cent were found to be ulcers by the pathological department
- 4 The teaching of early diagnosis and immediate operation in carcinoma of the stomach has offered very little as to ultimate cures in this disease during the past two decades
- 5 From the evaluation of our statistical data from Bellevue Hospital and Post-Graduate Hospital, the patient with the short history has no better chance of a permanent cure than the one with a long history
- 6 The suggestion of a hormone connection between the estrogens androgens and gastric mucosa as a possible factor in carcinoma of the stomach is based on the review of the recent work by many authors

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ACUTE SURGICAL CONDITIONS OF THE ABDOMEN IN CHILDREN*

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THE acute abdominal conditions in childhood differ materially from those of adult life as regards type of lesion, diagnosis and treatment. We have made a study of these abdominal conditions as they have appeared on the Children's Surgical Service of Bellevue Hospital, to which are admitted children up to the age of thirteen. The lesions may be divided into obstructive lesions and inflammations.

Congenital obstructions of the gastrointestinal tract are about the first to be brought to the attention of the surgeon and those of the upper part are the best known. The most common of these is congenital pyloric stenosis which has to be differentiated from the various types of duodenal obstruction.

The symptoms of upper gastrointestinal obstruction are typical. Vomiting begins early and soon becomes projectile in type. There is great distention in the upper part of the abdomen to correspond to the dilated stomach. Peristaltic waves can be seen and the bowels do not move. Because the baby is unable to retain any feedings he rapidly becomes dehydrated and emaciated.

In congenital pyloric stenosis the obstruction is due to the hypertrophied pyloric muscle which is sufficiently large to make a tumor palpable through the abdominal wall. The obstruction is not complete at first and does not become so until spasm develops in the pylorus. This happens usually about two weeks after birth, but may be earlier or later.

Duodenal obstruction may be of two types. The first is intrinsic due to a failure of the duodenal lumen to open properly and it may be a complete atresia from a plug of cells or from a diaphragm, or it may be a stenosis with a tiny lumen. The second is extrinsic and is associated with incomplete rotation of the gut producing obstructive bands or volvulus.

* From the Children's Surgical Service, Bellevue Hospital. Fenwick Beekman, Surgeon-in-charge. Given December 6, 1940 before the Section of Surgery of The New York Academy of Medicine.

The difference in pathology will establish the differential diagnosis between the upper abdominal obstructions. The vomiting of pyloric stenosis usually does not begin until after the second week of life, i.e., when the pylorus closes, although one of our patients developed symptoms on the day after his birth and another on the third day. The vomitus consists entirely of gastric contents as the obstruction prevents any regurgitation of duodenal contents such as bile. The pyloric tumor can be palpated, a sign pathognomonic of the condition and one which should always be found before operating.

When the obstruction is in the duodenum, vomiting begins shortly after birth and if the obstruction is distal to the papilla of Vater, which is the case in the majority of instances, the vomitus will contain bile. No firm tumor can be felt. If the meconium is examined, squamous epithelium will not be found as that which is characteristically present in meconium arises above the obstruction.

X-ray will help in the diagnosis as the gas-filled stomach will show on a flat film when the obstruction is pyloric, while the duodenum will be seen as well when the obstruction is duodenal. Contrast medium such as barium should not be employed as it may obstruct the stoma should anastomosis prove necessary.

Pyloric stenosis predominates in males in the ratio of 5 to 1 and shows a distinct familial tendency. Duodenal anomalies are apt to be associated with congenital anomalies elsewhere.

Pylorospasm occurs in early infancy and may resemble obstruction. It is not as severe as obstruction, it is intermittent and it can be relieved by atropine and thick feedings. The tumor pathognomonic of pyloric stenosis cannot be palpated.

Congenital obstructions of ileum or jejunum have much the same etiology as those of the duodenum and are decidedly rare. The vomiting commences a little later than in duodenal obstruction and the distention is much more extensive, involving more than just the upper abdomen.

Surgery is the treatment of all these organic obstructions and it should be undertaken at the earliest moment compatible with safety. To operate on an emaciated, dehydrated baby with a distended stomach is to court disaster. The fluid and electrolyte balance should be brought to normal and transfusion given if necessary. The stomach should be emptied by lavage before operation. It may require 2 or 3 days to get the baby in condition to undergo operation but it is time well-spent.

For anesthesia we prefer drop ether unless there is some contraindication. In that case we use local anesthetic of 0.5 per cent procaine. We employ an upper right rectus incision sufficiently high to overlie the liver. Robertson¹ has recently advocated a right subcostal incision which appears to have some advantages.

The operation for pyloric stenosis is the Fredet-Ramstedt procedure introduced into this country by Downes² and ably described by Donovan,³ Robertson¹ and others. Further description is unnecessary. One point deserves mention, however. Opening the duodenum at the distal end of the tumor is an accident which easily happens. Great care should be exercised to avoid it but if it should occur no damage will result provided the opening is immediately closed with fine silk. The Fredet-Ramstedt operation properly done carries a low mortality and effects a complete cure.

The operation for duodenal obstruction is a more serious procedure and has a high mortality. Occasionally it is possible to relieve extrinsic obstruction by cutting a band or correcting a volvulus but usually a much more extensive operation is required. A diaphragm may be cut if that is the cause but in most instances it is necessary to perform a duodeno-jejunostomy. This is tremendously complicated by the contracted condition of the gut distal to the obstruction. Ladd⁴ has reported several cases successfully treated by this method and recently Stetten⁵ reported another in a premature infant.

Obstructions farther down in the small gut are treated by some form of entero-anastomosis. Sometimes the obstruction is the result of inspissated meconium in a stenotic portion of the gut, in which instance it is necessary to open the gut and remove the obstructing agent.

Atresia ani, next to pyloric stenosis, is the most common congenital alimentary tract obstruction. It is easily recognized by the fact that the baby does not pass meconium. According to Ladd and Gross⁶ there are four types: two near the anus due to incomplete rupture of the anal membrane or to persistence of the anal membrane, and two higher up with the rectal pouch separated from it by considerable tissue. In one of the last forms the anal pouch is well formed and unless digital examination is made, the obstruction is not evident. X-ray examination not earlier than 36 hours after birth with the baby inverted will show the rectum filled with gas. If made earlier, or if the baby is not inverted, the gas will not be in the rectum. The anal sphincter is usually present.

In the treatment of these cases colostomy is to be avoided if possible. The rectal pouch is allowed to distend and then the operation is done from below. The sphincter is cut across by an antero-posterior incision and the dilated rectum mobilized by blunt dissection. It is then brought down, sutured to the sphincter and opened.

Congenital anomalies in this region are frequently associated with fistulous connections between rectum and genito-urinary tract but they do not produce obstruction and are mentioned here only in passing.

These congenital obstructions give symptoms early in life. Another obstruction arising later, but none the less peculiar to infancy, is intussusception. This is not a congenital defect, its etiology is obscure and the diagnosis is more often missed than in pyloric stenosis. Perhaps this is because the textbooks give a positive description that is not always present.

The textbooks describe a baby, usually between 6 months and 2 years suddenly seized with severe abdominal pain and vomiting followed by shock and prostration. He passes a fecal stool followed by blood or blood and mucus and then the bowel is obstructed. On examination a sausage-shaped mass is felt in the abdomen and often by rectal examination. This description is essentially true but by the time the baby reaches the surgeon the picture may have changed.

In the majority of our cases the chief complaint was bloody stools and sometimes diarrhea. The history of vomiting and pain could be obtained from the parents but only by questioning, as these symptoms had ceased. Mass was felt in only about half as it was obscured by distention, and when it was felt by rectum the condition was advanced and most of the patients died. Instead of a child writhing in agony he appeared to be a healthy infant quietly sleeping. More than once I have had the anesthetist ask if the wrong patient had not been sent to the operating room. The decision to operate should be made on the history as well as on the present findings.

Preliminary treatment is of as much importance here as in pyloric stenosis but because of the danger of gangrene of the intussusceptum it must be hurried and the operation performed at the earliest safe moment without waiting for the maximum improvement. The administration of fluids can be continued during and after the operation.

The intussusception involves terminal ileum and cecum or colon in most of the cases. It is usually single but some we have seen were com-

pound, i e., more than one intussusceptum was found in a single intussusciens. Gangrene of the bowel was present in about a third of our patients, all of whom died.

A right rectus incision is made regardless of where the mass is felt, as in practically all cases the intussusception starts on the right side and it is in this location that the greatest difficulty can be expected in reducing the intussusception. The reduction is made by milking out the intussusceptum rather than by traction which may rupture the delicate gut. In a few instances, however, a little careful traction may be a valuable assistance in the milking process but it should be done with the utmost gentleness and stopped at the first sign of resistance. An air enema, as practised by Farr,⁷ given in the operating room with the abdomen open, may help to start the reduction or even accomplish it. This should be done only as a surgical procedure under direct vision because of the danger of rupturing the gut.

When gangrene is present, the surgeon has no choice but to resect the gangrenous gut although most resections result fatally. Infants and children tolerate ileostomy or colostomy so poorly that resection is the method of choice and there have been numerous successful resections reported. Dowd^b reported one in a four year old boy in 1901 and another in a five day old baby in 1912.

Bleeding from the bowel may simulate intussusception when associated with gastrointestinal symptoms. Henoch's purpura is the principal disease to differentiate, but a bleeding Meckel's diverticulum may cause confusion, and bleeding by rectum in congenital syphilis obscured the diagnosis in one of our cases.

Strangulated hernia is another cause of intestinal obstruction. It is infrequent and when it occurs in childhood usually appears during the first two years of life. We have never had to resect the gut for this condition and in correcting the hernia simply ligate and remove the sac without attempting any sort of repair. A loop of gut twisted around an attached Meckel's diverticulum may also cause obstruction.

The inflammatory diseases of the abdomen in children may be divided into those without associated peritonitis and those with peritonitis. Obviously an inflammatory disturbance may start without peritonitis and develop it later but it will simplify matters to discuss them separately.

The condition for which early operation is imperative is acute appen-

ditus The typical syndrome of abdominal pain localizing in the right lower quadrant, followed by nausea and vomiting, tenderness over McBurney's point, fever and leukocytosis is known by every surgeon to be subject to variations In childhood the symptom complex is even more variable and is easily confused with the onset of certain systemic diseases or with other abdominal inflammations

The systemic diseases offer the least trouble although fully a third of the cases that are admitted to our service as acute appendicitis fall in the systemic group The child is more prostrated, the temperature is higher, the abdominal pain is vague and the tenderness is indefinite and slight Vague abdominal symptoms with a temperature above 103 seldom mean appendicitis and a little delay will serve either to clear up the symptoms entirely or to permit them to develop into those characteristic of the disease Pneumonia, scarlet fever, tonsillitis and upper respiratory infections are the ones most often found

Local retroperitoneal or intraabdominal inflammatory conditions present more difficulties and it is often quite impossible to make the correct diagnosis without operation Pyelitis, perinephric abscess or cystitis frequently simulate appendicitis and the urine examination, while usually sufficient to establish the diagnosis, may show nothing if the ureter is obstructed In this connection it is well to remember that a low-lying acutely inflamed appendix may be close enough to the bladder to cause urinary symptoms

Osteomyelitis of the ilium occurred in one of our patients and so closely resembled appendicitis that operation was performed With the abdomen open the true nature of the trouble was manifest

The pelvic inflammatory conditions of little girls are the easiest to differentiate Salpingitis secondary to vaginitis and pelvic bleeding from rupture of an ovarian follicle or backflow secondary to an imperforate hymen are not particularly uncommon but rectal examination, examination of the vaginal smear and a consideration of the age of the patient will usually make the diagnosis

Of the acute inflammatory conditions of the bowel acute Meckel's diverticulitis and acute regional enteritis must be considered A history of bleeding from the bowel may help with Meckel's diverticulitis but in any case operation is indicated and the diagnosis becomes of academic interest only With acute regional enteritis the differential diagnosis is almost impossible and in all of our cases was made in the operating room

They were treated by appendectomy and fortunately none went on to the chronic form of regional enteritis. Neither of these conditions is particularly common.

Mesenteric lymphadenitis is common, however, and is the worst stumbling block in differential diagnosis. In general the symptoms are a little less severe than those of appendicitis and the localization of pain and tenderness more or less indefinite. We usually make the diagnosis in the operating room, however, and remove the appendix as a routine procedure. We do not consider mesenteric lymphadenitis a clinical entity any more than lymphadenitis elsewhere in the body. I believe that it arises from the lymph drainage of infection or toxins in the area drained by the mesenteric nodes and is as protean as the area it drains and the infections thereof. For this reason I believe, contrary to Sobel and Stetten,⁹ that removal of these nodes is fraught with danger. It has been done many times by many surgeons and neither culture nor pathological examination has shed any light on the situation, but I have seen three cases in which peritonitis followed removal of the nodes, in one of which death ensued and in another chronic invalidism after many enterostomies and laparotomies for obstruction. Being therefore useless and dangerous it is the perfect example of meddling surgery.

Of the inflammatory conditions noted, the treatment for appendicitis and Meckel's diverticulitis is operation, for the others, symptomatic. When the diagnosis of appendicitis is clear-cut there is little difficulty. This happens in only about half of the cases, however, so some other criteria must be established for surgery.

We place most importance on localized right lower quadrant tenderness, especially if the psoas sign is positive or if there is rebound tenderness. History is of next importance with pain and vomiting in their proper sequence. Fever and leukocytosis are of value when taken in conjunction with other evidence. A gangrenous appendix with little or no fever or leukocytosis is a common occurrence. Rectal examination should be done, but, except in older children, is of little value unless a mass is discovered. An adult finger in a child's rectum causes so much distress and active resentment that the examiner cannot tell whether the pain is due to the morbid process or the examining finger. When in doubt we consider that operation is the most conservative form of treatment. Furthermore, if a child gives a typical appendix history, even if abdominal signs are minimal, or if a child has more than one hospital admission

with the same indefinite abdominal symptoms, we operate. By following this course we make mistakes at times but we also find a great many acutely inflamed appendices which would otherwise have been missed, and we have never seen any harm arise from the unnecessary removal of the appendix under such circumstances.

Peritonitis is the most serious intraabdominal condition and has the highest mortality. That secondary to a perforated appendix is the most common form. The disease starts with symptoms that can be recognized as due to appendicitis and too often there is a history of catharsis. Pain, vomiting, rigidity and distention make the diagnosis obvious. Unless the child is in a very serious condition, we operate, but only after the fluid and electrolyte balances have been restored. The appendix is removed if that can be easily accomplished, otherwise the operation is terminated. If the condition is diffuse peritonitis we have been putting 4 to 6 grams of sulfanilamide into the peritoneum. Drainage is not practiced unless there is an abscess or unless it is not possible to remove the appendix. Only the peritoneum is closed, the remainder of the wound being left open and lightly packed with vaseline gauze. Our results have been highly gratifying.

Peritonitis associated with gonorrheal vaginitis is not uncommon although with the use of sulfathiazole it is rapidly becoming so. It resembles primary peritonitis but a vaginal smear will readily disclose its true nature. Operation is not indicated. The gonorrheal peritonitis will subside rather quickly but, should the peritonitis prove to have another etiology, waiting for the abscess to develop may be the best form of therapy.

Primary peritonitis is practically always due to pneumococcus or streptococcus and many observers claim that it is almost entirely confined to girls. This they explain on the ground that entrance of the bacteria is gained via the genital tract and support their contention by the fact that cervical smear will produce the organism in pure culture. Our figures do not altogether support this contention even though there is a preponderance of girls. We agree with Newell¹⁰ who divides primary peritonitis into three etiological groups, viz. idiopathic, that associated with pulmonary or upper respiratory tract infections, and that associated with nephrosis.

The idiopathic type may predominate in girls but in others the female preponderance is slight. When peritonitis develops after an upper

respiratory infection it is usually a week or more after the onset and the sore throat or running ear is improving. Streptococcus is the organism usually responsible for this type. When associated with nephrosis the peritonitis is not necessarily a terminal condition as some of our patients have been able to form an abscess which can be drained and they have recovered. Pneumococcus is the usual organism in these instances.

The evidence is so typical of peritonitis that the diagnosis is rarely in doubt but as the treatment depends a great deal on the causative organism it is necessary to determine this. If the patient is a girl, cervical smear may give the desired information, otherwise abdominal puncture may be employed.

Our experience with abdominal puncture has not been altogether satisfactory in that sufficient fluid to give the information desired has not always been obtained. Also, the possibility of perforation of the gut with the needle makes the procedure not altogether harmless. Ladd, Botsford and Curnan¹¹ advocate making a small McBurney incision and opening the peritoneum under local anesthesia. If the peritonitis proves to be due to the colon bacillus, the incision can be enlarged and the appendix removed. If not, the pus can be sucked off and sulfanilamide inserted. This procedure has much to recommend it but we have had no personal experience with it.

Opinion differs as to treatment. Some of our patients recovered after drainage of acute peritonitis, others recovered after allowing an abscess to form and then draining that, but the majority of them died. Our feeling at present is to avoid operation in primary peritonitis until the formation of an abscess which is then drained. If the abdomen is opened under the mistaken diagnosis of secondary peritonitis, the pus is sucked off, sulfanilamide inserted and the peritoneum closed without drainage. The remainder of the wound is left open and packed with vaseline gauze. The proper chemotherapy is then begun by mouth.

Preliminary administration of glucose and saline by vein or hypodermoclysis is always advisable. No dehydrated child should ever be submitted to operation and the restoration of the normal fluid and electrolyte balances may mean the difference between recovery and death.

SUMMARY

Acute abdominal lesions of childhood are either obstructive or inflammatory

The obstructive lesions occurring directly after birth are congenital, those occurring later are usually due to intussusception

The inflammatory lesions are usually associated with the appendix but other conditions frequently obscure the diagnosis Operation is the conservative treatment

Primary peritonitis may occur, in which instance the conservative treatment is to delay operation until the formation of an abscess and then drain

Restoration and maintenance of fluids and electrolytes is essential

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TREATMENT OF DISORDERS OF THE MENOPAUSE *

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THE onset of the menopause is a gradual process unless castration is induced either surgically or by radiotherapy. The physiological menopause therefore usually is preceded by a recognizable preclimacteric stage of variable duration.

The menopause is anticipated with dread by a large number of women, because they expect to lose their attractiveness (with appearance of wrinkles, gray hair, flabbiness, hirsutism), sex allure, physical vigor and shapeliness (obesity, angularity). They likewise anticipate a diminution of libido and of mental capacity. They look forward to being harassed by discomforts such as flushes and sweats, headaches, diminished eyesight. Many of these fears, instead of being allayed, are further exaggerated and fixed by the attitudes and convictions of their family physicians.

Preclimacterium Preclimacterically, and I must emphasize that the preclimax may extend over several years, ovulation becomes less regular or may fail to take place. In consequence, continuous and excessive follicle growth may supervene, causing excess production of estrogens. If this excess is destroyed or excreted with sufficient rapidity, as happens in the majority of women, the individual remains symptomless. If the excess accumulates in the circulation, the symptoms of what I have called "premenstrual tension" develop, if the excess is excreted periodically, menorrhagia and metrorrhagia result. Characteristic of this stage are the uterine findings in such individuals. The uterus shows symmetrical enlargement, at the onset, the uterine muscle is soft and boggy, in the later stages, the muscle becomes hard and fibrous. In both stages the endometrium is found thick, edematous, sometimes polypoid, although occasionally very thin endometria are encountered. Microscopically such endometria show hyperplasia, not infrequently cystic dilata-

tion of the glands. At other times the glandular pattern is adenomatous.

Let me warn you that estrogenic therapy, so often resorted to at this time, because many of the patients have mild flushes, is not helpful and may prove harmful, by increasing the menorrhagia as well as the irregular timing of the cycle. It should be remembered that neurovascular symptoms are noted, not infrequently, in patients long before the menopausal years, and in themselves do not signify a premature menopause. This should be emphasized because, when flushes and amenorrhea develop in patients between thirty-five and forty-five, many practitioners habitually make the diagnosis of "premature menopause," an infrequent condition (at most in 4 per cent of women). Moreover, patients who have flushes coincident with amenorrhea, are not relieved by estrogens. Under such conditions, small doses of phenobarbital and repeated reassurance are usually adequate.

Clinical. When the menopause develops (this rarely happens before the forty-seventh to fiftieth year, and in women with fibroids even later) very definite changes ensue. These changes are both constitutional and local but should not be confused with the systemic changes incident to advancing years. Sudden and definite amenorrhea develops in less than 15 per cent. The majority show irregularity and increasing intervals between menstruations so that no exact time of onset can be recognized.

Physiological Changes. The most evident, readily recognizable constitutional changes are hormonal and are due to the unopposed and excessive action of the prepituitary or adenohipophysis which thereupon secretes an excess of the gonadotropic factor or factors. This excessive and continuous secretion and excretion can be determined readily by investigation of both the blood and the urine. If the ovaries are examined at this time, and this happens not infrequently during laparotomies performed for valid indications, they will be found to be smaller, fibrous, less vascular, and diminished in weight by one-third. The ovaries contain few or no cystic follicles, and no corpora lutea. As a result, a diminished estrogenic secretion is found both in the blood and in the urine. In many instances the estrogens have disappeared completely. The gonadotropic factors, as stated, characteristically are continuously present in large amount.

There is no evidence that I can accept, showing that other prepituitary factors such as the growth, thyrotropic or adrenotropic are af-

fects Likewise, there appears no change definitely ascribable to the climax in blood pressure (except greater temporary variability), metabolism or other general bodily functions This has been investigated repeatedly in young individuals who have been subjected to castration

Constitutional Symptoms The symptom complex associated with the menopause is characteristic The symptoms may continue for a shorter or longer period They will be most stormy in nervous, neurotic and imbalanced women, and less marked in the well poised and stable individual

The symptoms intimately associated with the menopausal condition are neurovascular, digestive, arthritic and psychical in addition to the local involutional changes Frequently one or more are complained of by the same patient By far the most common and best known to the laity are the neurovascular flushes and sweats, headaches and dizziness These may be extremely disturbing, embarrassing and even disabling The flushes and sweats awaken the patient at night and cause her to catch cold The headache and dizziness produce a feeling of insecurity, in extreme cases inducing the patient to stay at home and lead a hermit existence The digestive symptoms usually are mild eructations, sudden, variable and unaccountable abdominal distention, increase in constipation, nausea

The arthritic symptoms are vague Joint pains are experienced, especially of the metacarpo-phalangeal and metatarso-phalangeal joints, also of the vertebrae, less often ankle, knee and shoulder When I have had the opportunity of examining previous x-ray films of a somewhat earlier date, and comparing these with more recent films, it became apparent that the pain is not due to any increased bone changes recognizable by x-ray

The psychiatric symptoms as a rule are mere exaggeration of the previous overt or latent tendencies existing in the individual Such complaints as unrest, emotionalism (lacrimosity, depression), inability to concentrate, irritability, quarrelsomeness, loss of self-control, become more marked and may then first be noted by family or relatives As Heaver phrases it, "Such a woman is much more susceptible to minor insults to her pride and ego, and certainly she experiences more difficulty than ever before in coping with these" In a small number of patients, real psychoses develop, in the form of involutional melancholia and paranoid manifestations

Local Symptoms The local symptoms of involution or atrophy are mild. The breasts involute, showing atrophy in thin individuals and increased replaced accumulation of fat in the obese. Women with a tendency to obesity quite often at this period note a temporary redistribution of fat producing an enlargement of the hips and of the abdomen. The pubic hair eventually thins out and becomes gray. The labia majora lose their plumpness, the minora shrink and evince pallor. The vagina becomes less succulent, dryer, and paler, but coital disturbances rarely develop. The cervix, particularly the portio, involutes together with the uterus, the entire organ appearing smaller, thinner and rubbery in consistence. The involution of tubes and ovaries cannot be elicited by palpation. Vaginal and cervical secretion diminish. The vaginal smears may show a characteristic menopausal type although this is not the case in a considerable percentage of patients, if spreads are stained with fuchsin or hematoxylin eosin. It should be emphasized that with few exceptions, myomata of the uterus diminish markedly. Myomata which originally were no larger than a tangerine, as a rule, two or three years after the onset of the menopause, can no longer be recognized. Therefore small fibroids first noted in women of forty-five years, rarely require surgical removal.

MENOPAUSAL DISEASES

While discussing the local changes, it is well to mention the pathological changes which fall into the frame of menopausal diseases.

Semle Vaginitis, manifesting itself by burning sensation, rarely produces actual pain, and is recognized by red, punctate subepithelial spots, and the development of synechiae in the fornices. The vaginal secretion is scant, colorless and alkaline.

Pruritus is recognizable only by scratch marks. *Leukoplakia*, superficial white, discrete areas anywhere on the visible mucosa from the labia minora inward, is due to thickening of the superficial epithelial layers (hyperkeratosis). *Kraurosis vulvae* is a shrinkage of the labia minora with epithelial atrophy, fissuring, often accompanied by leukoplakia, and in 50 per cent of the patients eventually changing into carcinoma. It should be added that while pruritus, leukoplakia and kraurosis are found in the menopause, the same syndromes occasionally, but much more rarely, appear long before the preclimacterium has set in.

As to corpus carcinoma and ovarian malignancies, it is even more

difficult to determine whether the menopause or the age group is the main determining factor for their greater frequency. I am inclined to think that age is of greater importance. So-called functional ovarian tumors, particularly granulosa cell tumors, through their internal secretion, produce recurrence of bleeding and are therefore more readily recognizable in the menopause. Whether the frequency of carcinoma of the breast in this group has any direct connection with the menopause, I must leave an open question.

On the other hand, I have found no convincing evidence to support the hypothesis that arteriosclerosis and cardiorenal diseases have any direct connection with the climacteric changes, particularly as even in the early stages they do not respond to estrogenic therapy. The same may be said of obesity which to a large extent is due to the emotional factors which so strongly tinge the entire outlook of the laity and produce a self-imposed sluggishness and depression in many individuals. It is true that some investigators have declared that sugar tolerance is decreased and adrenalin sensitivity increased after the menopause.

TREATMENT

Although all women who survive, eventually reach the menopause, not more than 15, or at most 20 per cent are incommoded sufficiently to seek relief. Of those who consult a physician, a considerable proportion have mild symptoms, for the control of which full reassurance and non-specific medication will suffice.

Non-Specific Treatment of the Menopause The advice should consist of a description of the situation. The patient should be told that if the symptoms do not increase, very little treatment will be necessary, and certainly that no hormonal treatment, such as injections, of which the laity is now fully aware, will be needed. If the patient is overweight, she should be cautioned and placed on a detailed, mild, reducing diet. The carbohydrates and fats should be restricted, and the patient should weigh herself once a week. Sufficient exercise, preferably walking, should be indulged in. Frequently, measures to relieve constipation are likewise indicated.

For the mild flushes and sweats which annoy the patient, mostly at night, one-half of a grain of phenobarbital before retiring, may be prescribed. Occasionally one-quarter of a grain may be necessary during the day time. The sedation should be regulated below the dosage at

which day time sleepiness is induced

The majority of these patients will seek advice at intervals because they are disquieted by their gossiping friends as well as by the articles which they read in the newspapers or magazines, with consequent re-awakening of their fears

Specific or Replacement Therapy Particularly after the induction of the menopause by surgical castration or by x-ray, the symptoms may prove stormy and severe. This applies most frequently to young nervous women. Occasionally some of the patients, in whom the non-specific therapy just described has failed, may likewise demand further aid. Complete relief of symptoms is attained by natural or synthetic estrogenic substances. In my experience, less than one per cent of patients do not respond to the estrogens

Pharmacology of the Estrogens Today the estrogens may be obtained as pure chemical entities. Their characteristic is induction of artificial estrus in laboratory animals (mainly rodents). The estrogens exert their effect upon the uterus, vagina, vulva, Fallopian tubes, as well as upon the breasts. Immediately after the beginning of absorption, temporary local, as well as slight peripheral vasodilatation manifests itself. The contractile response of the musculature of the uterus and tubes which was abolished or diminished by castration, returns. The uterine mucosa undergoes changes due to the stimulation. The vaginal spreads change to the estrual type. Similar effects are produced in the human being by sufficient dosage. The vaginal spreads show definite and recognizable changes. The response to estrogen continues until the drug is withdrawn or eliminated. In addition, in the human being, as the result of effective estrogenic therapy, a readily recognizable disappearance of the gonadotropic factors in the urine is demonstrable by simple laboratory tests

In the rodent, long continued exhibition of estrogen produces enlargement of the prepituitary, and in susceptible strains of mice, adenocarcinoma of the breast. In the guinea pig, diffuse fibromyomata of the uterus and peritoneum may develop. Analogous results have not been recorded in the human being

Available Estrogens More than one hundred active pharmaceutical products are on the market. I do not consider it my function to single out a given product. The estrogens may be used in a number of ways. An unnecessarily popular form of exhibition of the drug is by subcu-

aneous or intramuscular injection. The estrogens must be dissolved in oil as their water solubility is minute. Since this method of medication has become so popular, I have seen a number of patients who develop a sensitivity to the oily medium, producing severe local allergic reactions and necessitating the stoppage of this form of giving the estrogen. Some of the estrogens are absorbed by mouth, particularly estriol and estradiol. Absorption likewise takes place through the vagina and through the skin. Recently, implantation of crystalline estrogens subcutaneously has been tried (As a rule, such implantation necessitates a small incision, under local anesthesia, and suture of the wound). In the great majority of cases the estrogens may be given by mouth. It is to be remembered that during absorption a considerable portion of the drug is carried off in the intestine and destroyed by the liver, and, therefore, the dosage must be increased ten times above that used for injection.

Unitage of the Estrogens At the present the dosage is in a state of confusion which misleads practitioners unnecessarily. The generally accepted and basic unit is the international unit of estrone (I U). This is arbitrarily 0.1 of a gamma or 1/10,000 of a mg. of estrone. This roughly corresponds to 1 M U, a quantity which will produce full estrus in a castrated mouse. There is a benzoate unit which corresponds to 0.1 of a gamma of estradiol benzoate. This unit should be abandoned. Many of the pharmaceuticals are based on the Rat Unit (R U) which roughly corresponds to 5 I U. The commonly used estrogens may be grouped as follows according to their physiological effectiveness: Estriol—one-sixth of the effect of estrone, estrone—the unit, estradiol—five times as effective as an equal weight of estrone. This should suffice for any practical purpose.

For general purposes, tablets of estradiol in the dosage of one-half mg. of the active substance, three times a day, by mouth, is sufficient for the great majority of patients. I have seen no advantage in using the other forms of natural estrogens although for vaginal suppositories estrone is sufficiently strong.

The main objection to the continued use of estrogens is their high cost. This drawback doubtless will be overcome eventually by synthetic estrogens. In England and Canada, Stilbestrol, a synthetic estrogen, is permitted to be sold. Its price is less than one-tenth of that of the natural estrogens. As yet, the Food and Drug Administration has not authorized its sale in the United States. This is largely due to the fact

that approximately one out of ten patients develops nausea as a result of taking the drug and that when given in large doses, liver damage has been said to result

METHOD OF USE OF ESTROGENS IN THE MENOPAUSE

I hope that in what has preceded, I have sufficiently cleared the decks to describe the actual use of estrogen in given cases of the menopause. By this medication it is usually possible to abolish rapidly the flushes, to relieve digestive disturbances and, in most cases, to lessen the arthritic pains. Usually, too, these patients experience a feeling of well-being and increased physical vigor. Rarely an increase of libido is noted. I have seen no convincing evidence that high blood pressure is influenced or relieved.

It is my practice to prescribe thirty tablets, each containing one-half mg. of alpha estradiol. These tablets are to be taken at first three times a day, a half hour after each meal, until the flushes definitely improve or cease. In the average patient this occurs after four days. The patient is then told to take only two tablets a day, one in the morning and one in the evening, until the last three tablets are reached. Then the patient takes but one tablet in the morning for three successive days. By this gradual withdrawal, annoying bleeding in patients who have their uteri, usually is avoided. The patient is directed to take no further medication except one-quarter of a grain of phenobarbital, twice daily. With the first reappearance of flushes, a similar course of estrogenic treatment is repeated. The aim is to lengthen gradually the withdrawal periods until no recurrence of symptoms takes place. No definite prognosis as to the duration of the condition can be given. In general, it may be said that the more nervous the patient, and the more frequent and severe the flushes, the longer will active menopause symptoms continue, but as this may cover a time anywhere between six months and six to ten years, it is unwise for the physician to predict.

In my hands this type of medication has been successful in the vast majority. I have not resorted to the overpopular method of injection for several years. Injections cannot be carried out indefinitely without the patient eventually rebelling. As previously mentioned, allergy to oil may necessitate resort to other methods. Abscesses and granulomata have occurred. If injections are resorted to, the best type of medication is estradiol benzoate, obtained from a reliable firm. The injection should be

given twice or thrice weekly until the flushes are fully abolished. The individual dose is two thousand Rat Units. After the flushes are under control, weekly injections are resorted to. Under this type of medication, irrespective of their age, annoying uterine bleeding is much more apt to occur in patients in whom the uterus has not been removed. I have seen it in a woman seventy years old, and therefore patients should be warned of this possibility, in order not to be unpleasantly surprised or alarmed. Some endocrinologists feel that the psychic effect is greater when injections are resorted to, but unless we are entirely mistaken in our concept of estrogenic therapy for the menopause, no psychotherapy is needed.

I see no advantage in attempting to give estrogen treatment by means of inunction. It is true that the estrogens are readily absorbed by the skin. However, it is impossible to gauge the dosage as accurately as by the other routes. Moreover, we are as yet unable to exclude definitely a potential local carcinogenic effect in the human.

The advocates of implantation have stated that the absorption by this method is more continuous and that an implantation effect may last for one to three months or even longer. Sterile crystalline estradiol is compressed into small tablets and by an incision, placed in the subcutaneous tissues. The rate of absorption varies according to the density of the pellet, the surface area exposed, and the greater or lesser connective tissue reaction which encapsulates the pellet. Once introduced the dosage is no longer under control. How successful the instrument devised by Thorn for implanting other types of steroids will prove to be in avoiding the necessity of scarring incisions, I cannot state from personal experience.

Vaginal suppositories containing from one thousand to two thousand International Units likewise cause absorption of estrogens. The suppositories are placed deep in the fornix by the patient before retiring. The patient wears a napkin until morning and then takes a cleansing douche. I resort to this type of medication mainly when a senile vaginitis causes annoying irritation and discharge, and the constitutional symptoms are mild.

In the last few years great enthusiasm has been shown by psychiatrists for the estrogen treatment of menopausal psychoses, particularly melancholic and schizophrenic manifestations. It seems to me that the primary enthusiasm will gradually evaporate. There is no question that

the menopausal symptoms can be abolished, thus affording some relief and inducing marked hopefulness in some of these women. However, I doubt that cure of deep-seated and well-developed psychoses can be anticipated. However, there is no reason whatever why such medication should not be tried under careful and critical supervision.

Contraindications Although in my opinion the use of estrogens is much overdone and is not at all indicated in the preclimacteric period when menstruation still occurs, there are actually few other contraindications for the use of estrogens. Estrogens should not be used postoperatively in patients in whom endometriosis has been found. The same applies to patients operated upon for carcinoma of the breast, or either operated upon or treated by radiation for carcinoma of the cervix and carcinoma of the uterine body.

Another mainly climacteric disease, namely kraurosis of the vulva, has been treated by estrogens. This condition is an atrophic one and usually a sequence of the menopause. In my experience, fully 50 per cent of kraurosis of the vulva changes into carcinoma of the squamous type. Knowing the definitely carcinogenic potentialities of estrogens, it seems unwise to further complicate the situation by giving estrogens in any form, particularly by localunction. I am further encouraged in making this contraindication absolute by the fact that I employed the method years ago when carcinogenesis and steroids were not at all associated, and found that any change or relief obtained was of purely temporary nature.

It is my hope that I have been able to clarify for you some of the confusion and misconceptions which becloud this as yet new therapeutic treatment. Those of us who have been interested in endocrinology for many years consider the estrogenic relief of the menopause as a major triumph, second only to that of the treatment of hypothyroidism by thyroid medication and of diabetes by insulin.

MEDICAL TESTIMONY IN PERSONAL INJURY ACTION *

The Honorable WARNICK J. KERNAN

Chairman New York State Law Revision Commission

IT is conceded, I believe, at the outset of our discussion, that medical testimony, in the so-called personal injury action, involves an evil which seriously affects the administration of justice. The causes of the evil must likewise be conceded. In their consideration, three important elements are generally found to be present, each one of which is a contributing factor, namely the opportunity for the doctor to predicate his opinion on subjective symptoms, which induces exaggeration, if not worse, on the part of a claimant, the very natural tendency on the part of a doctor, by whatever party to a lawsuit retained, to become a partisan in the action, whereby the skilled adviser loses that disinterestedness, without which the testimony of any witness is so readily colored, and the contingent fee contract of the lawyer, made necessary, in so many instances, by the circumstances of the client, which provides a stake, in the way of remuneration, out of all proportion to the service arousing as it so often does his cupidity and breaking down all resistance against unethical practices. With claimant and lawyer both in a position to benefit from the size of a verdict, there is an ever present temptation, difficult to combat, and it is not surprising to find an exaggeration, in very many cases, which frequently takes on the aspect of fraud, as well as doctors whose opinions are purchasable. As a result, expert testimony, in the kind of action we are considering, has gained such a disrepute that very many medical men will refuse to become identified with either party, whether plaintiff or defendant, and a cynical public, seeing the perjured cause prosper, becomes contemptuous of a profession which permits it, and is weakened in its respect for the courts. Arguing from the one type of cause, it reaches the wholly un-

* Read February 25, 1941 before The Association of the Bar of the City of New York in the symposium in cooperation with The New York Academy of Medicine and the Medical Society of the County of New York.

justifiable conclusion that every lawyer, in every case, is moved by an interest which knows no deterrent to a successful outcome, that false testimony is not merely condoned, but is encouraged, and that the judge, whose function is to promote the administration of justice is indifferent to the spoken lie in his presence, or without courage in its rebuke

This statement of the evil with which we are confronted, and its effect, will not be seriously challenged, and if the prestige of our courts is to be maintained, there must be some affirmative action upon our part. A plea of helplessness by the profession is an admission that our judicial system is lacking in that vigor which is essential, if it is to continue to exist. It is more than that—it is an invitation to take increasingly from the courts the jurisdiction which the courts have for so long enjoyed in the determination of legal disputes.

If the tendency of the last twenty-five years to create departmental boards or agencies for the adjudication of specialized questions is not explained by the abuse of expert testimony in the personal injury action, the abuse has at least made easier the trend, and the task of the lawyer, in effecting administrative reforms, is made more difficult. It may seem a far cry, but, as much as anything else, the excessive growth of departmental boards and agencies bespeaks a want of confidence in the law. Unless we can maintain such a standard of procedure that loose and perjured testimony is discouraged, and the perjurer is made to fear we lose the weight which might be expected to attach to our views, and our protest of the narrowed province of the courts and the lessened field of the lawyer, is of little avail.

It is not to be gathered from what I have said that conflicting opinions are always indicative of the abuse of expert testimony. Upon very many subjects involving skill and experience, exact conclusions are not to be had upon the same statement of facts, and searchers after the truth however honest their effort, will differ as between themselves. But there is the dishonest, the careless, and the indifferent expert to be considered, whose biased findings are always available to confuse the particular issue and to bewilder a jury, as well as a court.

The Law Revision Commission of the State of New York early recognized the evil which is inherent in expert testimony in the personal injury action, and in its 1936 program, there was included a proposed statute, designed to meet, or at least, to minimize the evil. Under its

terms, in any civil action to recover damages for personal injuries, the court, of its own motion, before or during trial, was empowered, in its discretion, to appoint a disinterested physician to make such a physical or other examination of the injured person, as might be necessary to form an opinion as to the nature, extent, or permanence of the injury. The report of the physician so appointed, was to be in writing, under oath, and was to be forthwith furnished to the judge, a copy to be furnished as well to the attorneys for each of the parties to the action. Thereafter, such physician might be called and examined as a witness by either party, or by the court, and he was made subject to examination and objection as to competence and qualification as any other witness, and as to bias, and might be cross-examined. The compensation of the physician, which is always a difficult problem in the devising of any plan, was to be fixed by the court, for the payment of which the parties were made jointly and severally liable, or the court might determine the proportion in which it should be paid by the parties, and any amount paid was made taxable and was allowed to a successful party, as any other cost. If any person paid or offered to pay, or accepted or agreed to accept, more than the compensation fixed by the court, it was made a contempt and punishable accordingly.

An added provision, which should be touched upon, was that the appointment by the court of a physician was to be "after a hearing to be attended only by the parties interested or their attorneys," it being assumed that any appointment would involve a discussion of personalities, as well as questions of compensation and payment, which might be better carried on if there was an absence of the publicity which would be attendant upon a discussion in open court.

Behind the statute suggested, there were two thoughts. The statute, in itself, would furnish to the court an effective means whereby, in a proper case, there might be brought to bear such an examination as would make possible the ascertainment of the truth. This possibility was evidenced, in my own experience a few years ago when an upstate judge, acting beyond his powers, announced to opposing counsel there had to be an examination by a physician of his own choice during the noon hour, the opposing doctors having contradicted each other as to an objective symptom or condition which could be ascertained with certainty, and when the court reconvened in the afternoon, the doctors had left, and what had been bitterly disputed, was an admitted fact in the

case More than this, even if the power vested in the court should not be exercised, its very possession would be in the nature of a check upon a medical expert A medical witness will be more thorough in his examination, more studied in his opinion, more careful in his utterance, and less prone to exaggeration, to say nothing of wilful misstatement, if he knows that at any moment the court may itself order an examination

A big stick in the hands of the court, in the situation we are considering, may be as effective as a big stick in the hands of the mythical individual, who was counselled by a former President to walk softly and never to be without it

Whether the power contemplated by the proposed statute would prove effective, would depend very largely upon the judge In the hands of a weak judge, it might be abused, or at best, it would not be invoked But in the hands of a competent judge, it would be an added power, and given sufficient power, there is no evil with which a court cannot adequately cope

Why there should be hesitation in the giving of the power, assuming the mechanics of any proposed statute are unobjectionable, is difficult to understand The determination of the issue in the case will still be with the jury The judge will still be restrained in commenting upon the weight of the evidence and the credibility of any witness, although, in my opinion, his enforced silence, in such respect, is one reason for the acuteness of the evil under discussion

New York has for so long enforced the rule, mistakenly, I think, that a judge, neither by word or act, is to influence even remotely a jury, that he is little more than a kind of glorified arbitrator between opposing counsel, to direct the course of a trial As lawyers, we all wish to win our causes, and there is a point beyond which in any trial, the interference of the court may be properly resented But the cause which cannot withstand the scrutiny of a competent judge, and his disinterested comment, is questionable, and it would make for a better administration of justice if both the questioned cause, and the unprincipled lawyer who pleads it, could be made to appear in their true light

In failing to legislate, the Legislature is not to be criticized The subject of medical testimony in the personal injury action is one in which the urge for legislation should come from the legal profession and any urge upon our part has been wanting It is one of our weaknesses that there are too many subjects upon which we are silent until an evil

has attained such proportions that the insistence for some reform comes from without

Neither is the Law Revision Commission to be criticized. Its function is to study and recommend, and this it has done. When a recommendation has been submitted, with its accompanying study, information is at hand, and for the Law Revision Commission to attempt to force its conclusion would be to invite a clash of opinion and threaten the value of its work. Beyond making a thorough and impartial study, the Commission has no interest to serve, and any recommendation must speak for itself.

Legislation affecting expert testimony, in an effort to insure a measure of certainty, is not a novelty. Already, laws have been enacted in New York, which affect it, to a certain limited extent, in matters having to do with criminals and the criminal law. Thus, under section 31 of the Judiciary law, in a criminal action or proceeding, or in habeas corpus or certiorari proceedings to inquire into the cause of detention, in which soundness of mind is an issue, the court may appoint not more than three disinterested competent physicians to conduct an examination, whose compensation is made a court expense, and any such physician may be sworn as a witness at the instance of any party. Sections 658 to 662-a of the Code of Criminal Procedure likewise provide that where the defendant in a criminal action pleads insanity as a defense, the court may appoint a commission of not more than three disinterested persons, at least one of whom shall be a qualified psychiatrist, to examine the defendant and report to the court as to his sanity at the time of the commission of the crime, and if the commission finds the defendant insane, the trial or judgment must be suspended until there is a return of sanity, provision being made, in the interim, for his confinement in an appropriate institution. Under section 870 of the same code, if a person in confinement appears to be insane, power is given to the court to commit to a state hospital, which is obligated to take proper measures for the determination of the question of insanity, or the judge may himself institute an investigation, calling two legally qualified examiners in lunacy, as well as other witnesses, whose fees are audited and allowed by the judge and paid for as a county charge. And under section 125 of the Mental Hygiene Law, any person alleged to be a mental defective, who is arraigned on a criminal charge, may be placed either before or after trial or conviction, in a hospital for examination, such examina-

tion to be made by two qualified examiners, or a qualified examiner and a qualified psychiatrist, who are paid in the first instance out of public funds. Upon their report, if the examination discloses that the alleged defective is of such a nature as to require supervision, control and care for his own welfare, or the welfare of the community, the judge is empowered to proceed accordingly.

Also in an action of annulment, independently of any statute, and solely upon the ground of public policy, in order to prevent collusion, the court has reserved to itself the right to direct the examination of a party by medical experts of its own choice, where physical incapacity is an issue.

In each of the legislative enactments referred to, it will be noted that a certain measure of responsibility is placed upon the judge in the sense that he is the motivating authority. The payment of experts is also within his control and is in the nature of a public charge.

Other jurisdictions, notably Rhode Island and California, have enacted statutes enlarging the power of the court upon the motion of the parties, and in California, upon the motion of the court as well, so as to include the appointment of experts in civil actions. Whether because of defects in the statutes, or because of an unwillingness on the part of the court to invoke the power conferred unless requested by the parties, there is a lack of convincing proof that the statutes have resulted in substantial benefit. In fact, in Rhode Island, the statute is a dead letter. In California, the views of the judges as to the worth of the California statute differ, some reporting that they use it only on the approval of attorneys representing all parties, others, that they have little use for it, and a few that they do not use it at all.

In England, under what are termed New Procedure Rules, the court is given certain broad powers in civil actions, but a study of the English statutes is not immediately helpful so far as our problem is concerned, because it seemingly permits the dispensing with a jury, which would give rise in this state to a constitutional question.

Any statute enacted must necessarily be experimental. As was said by the Law Revision Commission, in the submission of its proposed statute, is the proposed statute workable, and will it remedy abuse? Will the court avail itself of its enlarged powers? Are there weaknesses in the statute, and can it be strengthened? To what type of action, usually giving rise to expert testimony, can the statute be extended? When

sources of original information are no longer available, in what way will the disinterested expert be acquainted with the facts, which will insure an accurate finding?

These are only a few of the questions which can be asked. Others will readily suggest themselves. Provisions which are sound in theory may prove unsound in practice. It is only by trial and error that points of weakness in any statute can be uncovered. Whether a statute is practicable, serving any worth while purpose, can only be determined by use.

Even more important, assuming there is any legislative enactment—there must be the effective cooperation of the bar. A willingness to assist the court, in what must be an unpleasant and difficult task at best, will be in itself a long step forward in making any statute effective, thereby helping to overcome the evil at which the statute is aimed. Given the required tools, the bench, working with the bar, can bring to a disputed issue of injury such a measure of certainty, in very many cases, that the task of a jury will be lightened, and expert testimony, in the personal injury action, will cease to be a scandal and a reproach.

THE EVOLUTION OF CLINICAL
SPHYGMOMANOMETRY*

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THE pressure of the blood within its system of circulation has always been one of the major physiological manifestations of health and of disease. Knowledge of the behavior and significance of this pressure was, for long, slowly accumulated, and its development depended upon the evolution of certain techniques. The common clinical method of measuring the blood pressure by a mercury manometer and a stethoscope over an artery is a comparatively recent procedure, in fact more recent than clinical electrocardiography. A few remarks on its evolution may be of interest.

Though the circulation of the blood was established as fact by Harvey in 1628, and the pressure of blood in the circulation was shown in a measurable way by Hales in 1733, and the use of a manometer using fluid, either water or blood and later mercury, was well-known and employed in physiological circles in the latter half of the Nineteenth Century, the clinical technique did not evolve until after the turn of the century, and did not become widely used until thirty years ago. Yet, the art of simple palpation of peripheral arteries has undoubtedly existed as long as the art of medicine, the ancient physician, one can justifiably suppose, made crude but often significant deductions on the tension of the arteries, even before he realized the nature of the circulation of the blood. The exact formulation of such observations awaited the use of instruments of precision and a technique for their application. Janeway¹ expressed aptly this historical point when he wrote, "that the blood exerts pressure upon the vessels through which it circulates is, of course, a necessary corollary of the fact that it flows, but more than a hundred years elapsed before Harvey's discovery of the circulation was followed by Hales' demonstration of the blood pressure in 1733, and a second century before its accurate study was begun."

* Read November 13, 1940 in the Section of Historical and Cultural Medicine of The New York Academy of Medicine.

My purpose in this paper is the history of the concept of sphygmomanometry and of the introduction of its various techniques into clinical medicine, the development of the instruments has been considered elsewhere^{1,2} There are four techniques for measuring the blood pressure, in historical order they are the method of palpation, first without, later with, the use of a manometer, the method of direct measurement, the method of recording the oscillations of the pressure, and the method of auscultation

Simple palpation, without doubt, has been an old natural procedure It became of more value with the use of a manometer for recording the pressure necessary to obliterate the pulse, of which I shall say more later

In 1733, Hales³ introduced the technique of direct mensuration by placing a tube in the artery of an animal and obtaining the height to which the blood flowed, a procedure still employed widely today in modified form and primarily for physiologic investigation Yet a century elapsed before the accurate study of the blood pressure began, as Janeway pointed out, with the introduction by Poiseuille⁴ in 1828 of the device of mercury in a U-tube This procedure separated the observation of the blood pressure from the difficulties of large and unwieldy apparatus and provided the convenient facilities of a small instrument Also, with the use of an anti-coagulant substance, sodium carbonate, to keep blood from clotting in tubes, Poiseuille made prolonged experiments possible

Twenty years later, in 1847, the second major advance in accurate study was initiated by Ludwig⁵ with the invention of the kymograph Its application to indirect measurement of the blood pressure by the use of a pelotte placed over an artery and connected with a manometer and thereby dispensing with puncture of the artery, was suggested in 1855 by Vierordt,⁶ but his apparatus was unreliable as well as cumbersome, and the results too variable According to Brim,⁷ the device of Vierordt had been suggested by Herisson in France twenty years previously But Herisson's apparatus did not have the kymographic attachment, and, failing to become an established instrument, it did not spread the conception of a new clinical procedure The kymographic technique, though still using direct puncture of the artery and, therefore, restricted to measurement on animals, provided permanent records, permitted more objective observation and, with various modifications, afforded a wide

play for physiological study. From the work of this time especially by Marey,⁸ the manometric value of the pressure necessary to obliterate the pulse wave was shown to be a valuable criterion for measurement of the blood pressure. However, a suitable technique and accurate instruments for indirect measurements had not been developed. Sphygmomanometry had not yet become adaptable to man. It began to be so with the device of von Basch,⁹ introduced in 1876. von Basch's important contribution consisted of eliminating the direct puncture of the artery and the direct registration of the blood pressure by a column of fluid; instead, he used a bulb or pelotte at the end of a manometer to compress the artery of an extremity so that the wave of pulsation could be gradually eliminated and allowed to return. He introduced two new and fundamental principles, one, the pressure against the extremity and, therefore, the artery could be supplied by a bag containing fluid for compression, and, two, the connection of a mercury manometer to the bag would record the pressure necessary to compress the artery. In accord with these principles, a number of instruments were devised by von Basch, Marey¹⁰ and others. The chief modification by the former was the introduction of a portable metal manometer. More flexibility of use came in 1889 when Potain¹¹ replaced water with air for compression. His apparatus consisted of a bulb which was placed over the artery and inflated by a second bulb, the pressure was recorded in a portable metal gauge. Again, various modifications, such as by Mosso¹² to register the pressure in the fingers, and by Hürthle,¹³ were made in the device, using air for inflation, but the instruments were too complex for general medical use.

Though more easily performed, sphygmomanometry still remained unsatisfactory. The simpler apparatus gave erroneous results, the more complicated ones were too cumbersome. Furthermore, the von Basch-Potain procedure recorded pressure against the more solid tissues of the arm, as well as pressure directly on the artery.

In 1896, Riva-Rocci¹⁴ reported a convenient and more accurate device, on which the modern procedure depends. The method relied upon circular compression of the extremity. In his arrangement, a rubber bag was made to encircle the arm and was inflated by a rubber bulb, pressure from the arm band being registered in the manometer. The artery, therefore, was compressed at right angles from all sides equally and the application of pressure on non-arterial tissues only was avoided.

Riva-Rocci originally used an armband 5 cm wide, which was the source of some error. Being narrow, it depressed the tissues at an angle and pressure was recorded against the upper and lower shelf of tissues, as well as against the artery. This source of error was eliminated by the use of a band 12 or 15 cm wide, the advantages of which were demonstrated by von Recklinghausen¹⁵ in 1901, and a few years later by Stanton,¹⁶ Erlanger,¹⁷ Erlanger and Hooker,¹⁸ and Janeway.¹

Up to this time, the major criterion for the presence or absence of the pulse wave beyond the constricting band was palpation, palpation gave an accurate enough clue to the systolic or maximum level but did not indicate accurately the diastolic level and, therefore, the mean and pulse pressures. Furthermore, it required a trained sense of touch to appreciate the ebb and flow of the pulse wave. The oscillatory or visual method of taking the blood pressure with the air pressure cuff and manometer lessened the subjective error inherent in the palpatory technique but it was not a procedure adapted to rapid and accurate clinical work. The method depended upon the oscillations transmitted to the fluid in the manometer as the pulse wave came through the compressed artery, the appearance of definite oscillations denoted the first or systolic pressure, the change from large to small oscillations, the diastolic pressure. A variety of instruments, such as by Hill and Barnard,¹⁹ von Recklinghausen,¹⁵ Potain,²⁰ Erlanger,¹⁷ and Janeway,¹ were soon produced on the Riva-Rocci principle, they relied on the oscillatory as well as the palpatory method and employed either the mercury or the aneroid manometer. By devising an apparatus with a needle pressure gauge primarily for measuring the diastolic pressure shortly after Riva-Rocci's report, Hill and Barnard¹⁹ in England assisted materially in this period of advancement in clinical sphygmomanometry. Also, the more special instrument of Erlanger,¹⁷ employing the kymograph, provided not only accurate but written records of the oscillations of pressure in the air-pressure cuff as it affected the pulse wave. These instruments made possible investigations¹⁸ which established the value of both maximal or systolic and minimal or diastolic readings in the clinical appraisal of blood pressure.

The final step, however, which allowed full scope to, more accurate observation in, and a standardized technique for clinical sphygmomanometry came in 1905 with the introduction of auscultation, devised and reported by Korotkoff.²¹

I have taken particular interest in seeking the original reports of Riva-Rocci and of Korotkoff. Their articles were in journals of limited circulation. They have not been fully reported in English, and bibliographic references are often made inaccurately. I was able to find the original copy of Riva-Rocci's report and that of Korotkoff through the courteous assistance of three gentlemen—Dr Archibald Malloch, librarian of The New York Academy of Medicine, Mr Paul North Rice, chief of the Reference Department of the New York Public Library, and Colonel Harold W. Jones, librarian of the Army Medical Library, Washington, D. C. According to the Union List of Serials, the only issue of the journal containing Riva-Rocci's report known to be in libraries in this country is in the Army Medical Library, and the only available issue containing Korotkoff's report is in the Slavonic Division of the New York Public Library.

Riva-Rocci's report was given under the following title: "Un nuovo sfigmomanometro," *Gazzetta medica di Torino*, 47: 981-996 (no. 50, Dec. 10), and 1000-1017 (no. 51, Dec. 17), 1896. I should like to give a summary of a translation* of his report.

Riva-Rocci first recorded the purpose of his research on arterial pressure and then set forth the simpler aspects of hydraulics involved. He gave a fairly voluminous review of the literature and described the three types of the von Basch sphygmomanometer available commercially at the time. He preferred the first, or mercurial, model completed in 1881, to the non-mercurial manometer produced in 1883. Riva-Rocci adopted a modification of von Basch's instrument, which was similar to that proposed in 1881 by Rabinowitz, of which Riva-Rocci was not aware. Riva-Rocci's instrument was a "sphygmomanometer likewise based on the principle established by Vierordt and improved on by Marey and von Basch in turn. In other words, it is an instrument affecting manometric measurement of the force necessary to impede the progression of the undulation of the pulse. Sphygmomanometry is then applied to one of the large aortic branches, to the humeral. Since the humeral is the direct continuation of the axillary (since the region contains no collateral large enough to be considered as a branch of the bifurcation), the measurement gives the total charge of a point fairly close to the aorta or, if you like, of the charge of pressure either in the aorta itself (if the left humeral is concerned) or of the brachio-cephalic

* Translations of the articles of Riva-Rocci, Korotkoff, and Krilov were obtained through the facilities of the Library of The New York Academy of Medicine.

trunk (if the right humeral is concerned) " Riva-Rocci considered that his instrument was easy to apply, rapid in action, precise, and innocuous. It was composed of two parts, one for exerting pressure, one for measuring the pressure exerted. The compressor apparatus was represented by a tubular "muff" with walls soft, non-extensible, and impermeable to air. It consisted of a rubber tube 4 or 5 cm in diameter, lined with a cloth sleeve to prevent undue dilation of the tube. One end of the tube was open, while the other was attached to a piece of metal made in two parts. The patient's arm was tested with this tube plus an insufflator. The intercalation of a manometer revealed the pressure on the "muff" at all times, and hence the pressure exerted on the arm.

Riva-Rocci stated "The most reliable manometer is still the mercury manometer, but it is necessary to facilitate its reading by adopting a single branch, as in the manometers of Marey and of François Franc, and the original model of von Basch. In order to render the apparatus easier to handle and transport I, too, have adopted the metal manometer. So far I have been able to obtain only the holosteric kind, since the aneroid kind is of more delicate construction."

In order to prove that his instrument really measured the total charge of the arterial pressure, Riva-Rocci made a number of experimental observations, one series with artificial circulation inside rubber tubes, another with the cadaver arm, and a third with animals.

In the succeeding decade, clinical sphygmomanometry for the first time became a domain of increasing interest and of valuable application in the study of health and of disease in man. Considerable and fairly exact observations and deductions were carried out by physiologists such as von Recklinghausen, Hill, and Erlanger, and by clinicians such as Janeway. But the procedure and its interpretation were confined to a relatively limited medical group.

The opportunity for its wider application was soon offered. In 1905, Korotkoff¹ in Russia reported that by placing a stethoscope over the brachial artery at the elbow below the air-pressure cuff, sounds of the column of blood which flowed into the artery on release of the pressure became audible. Korotkoff's observations were given at a meeting of the Imperial Military Medical Academy in St. Petersburg, December, 1905 and reported in the bulletin of the Academy, "Izvestiya Voenno-meditsinskoi Akademii," page 365. The original report occupies only a portion of one page in the bulletin, with the title "On methods of

studying blood pressure (from the Clinic of Prof Feodoreff) " A translation in full reads

"On the basis of his observation, the speaker came to the conclusion that a perfectly constricted artery, under normal conditions, does not emit any sounds Taking this fact into consideration, the speaker proposes the sound method for measuring blood pressure on human beings The sleeve of Riva-Rocci is put on the middle third of the arm, the pressure in this sleeve rises rapidly until the circulation below this sleeve stops completely At first there are no sounds whatsoever As the mercury in the manometer drops to a certain height, there appear the first short or faint tones, the appearance of which indicates that part of the pulse wave of the blood stream has passed under the sleeve Consequently, the reading on the manometer when the first sound appears corresponds to the maximum blood pressure, with the further fall of the mercury in the manometer, there are heard systolic pressure murmurs which become again sounds (secondary) Finally all sounds disappear The time of the disappearance of the sounds indicates the free passage or flow of the blood stream, in other words, at the moment of the disappearance or fading out of the sounds, the minimum blood pressure in the artery has surpassed the pressure in the sleeve Consequently, the reading of the manometer at this time corresponds to the minimum blood pressure Experiments conducted on animals gave positive results The first sound tones appear (10-12 mm) sooner than the pulse which (1 ar radialis) can be felt only after the passage of the major portion of the blood stream "

This was the complete report It may be of interest to record the discussion at this meeting It was as follows

Dr An N Ivanov How do you explain the origin of the sounds below the sleeve in the beginning and in the end of the examination?

The Speaker (Dr Korotkoff) In this instance, the pressure in the sleeve is near the minimum pressure in the artery but still in the sleeve it is greater, with the blood stream slipping through, the walls of the vessel separate and give a short, flapping sound

Dr Ivanov What difference did you observe between the minimum and maximum pressure in the brachial artery?

The Speaker The differences varied greatly, but with a 25-35 mm norm and higher

Dr B G Bojowski If I understood correctly from your very interesting

report, you ascribe the origin of the sound phenomena in your simple experiment to purely local causes. The mechanism of the origin of murmurs is understood and does not need any explanation, but as to the development of sounds on the spot I cannot at all agree with you. Your explanation of the origin of sounds below the sleeve as a result of the sharp fluctuation in pressure, with all its appeal, cannot be considered the most important or possibly the only source of the sounds in the circulatory apparatus—the heart. Sounds which can be heard in some more or less large vessels are, no doubt, transmitted along the blood stream, which quite easily conducts these sounds from the closing of the semilunar valves of the aorta. In the nearest to the heart vessels, if they are intact, we hear the systolic tone after the closing of the valves, and in case they are damaged and inadequate, this tone becomes a murmur both in the aorta and in the vessels, for instance in the jugular and in others. Both the tone and the murmur are considered as conducted and not as local. Below the sleeve you cannot hear any sounds when the sleeve compresses the upper arm, probably due to the complete constriction of the brachial artery. In experiments on animals you did not hear anything even when the first drops of blood began to appear from a cut strip of artery with the diminished pressure in the sleeve. The sounds, the murmurs, and then again the sounds you perceive as soon as the flow of the blood begins, so to speak, to become pronounced, i.e., when the blood wave becomes so large that it becomes capable to conduct those sounds which originate in the heart. Your assumption of a local origin of the sounds in the vessels presupposes, one must say, active forces. Apart from the smooth musculature, we don't know of any active force in the blood vessels. And there is too little, or even complete absence, of it in such a vessel as the brachial artery to ascribe to it the origin of sounds in the vessel. Secondly, the time of development of sounds in your experiments coincides with the diastolic of the vessel, and such a state must be regarded as passive and not active. Besides, the blood pressure, by the fluctuations of which you are attempting to explain the reasons for the sounds, is in itself a complex conception. Apart from a certain tension of the blood vessels, blood pressure and its fluctuations in either direction is produced by the energy, by the force of the heart contractions. In view of the above, it seems that, even if there were any foundation for a discussion of the local origin of sounds in the blood vessels, it would still be impossible to deny their

origin in the heart. For the present, I repeat, this is their only source.

The Speaker First of all, I must say that the sound-tone in this instance is nothing else than the same compression murmur, however of such a short span that it is perceived by the ear as a sound-tone, indeed, the squeezing through of a minimal part of the pulse wave takes place in such a short interval of time (a fraction of 1 second) that it would be amazing if such a forcing would produce a murmur. But I also have reason to assume that the separation of the walls of the constricted vessel also takes part in the production of the sound-tones. Should we allow that the tones originate in the heart and are conducted, then the most favorable conditions for the transmission of these sound-tones should be the absence of any pressure on the pulse wave, i.e., listening to an artery which is not compressed, we should hear the sound-tones, however, under normal conditions this is not observed. Finally, the complete disappearance of the sounds with the complete constriction of the opening in the vessel also speaks against the fact that the sounds are transmitted instead of being of local origin.

Dr I P Shapovalenko The occurrence of murmurs and sounds under the gradual compression of an artery with a stethoscope has long been known. In your experiment, there was a gradual opening of the compressed artery and the sound phenomena, naturally, occurred in the reverse order, and there was noticed also a weak sound following the appearance of the murmur. Judging from your experiments on a dog, the first sound prior to the murmur appears after the passing of the first drops of blood through the compressed artery, much sooner than the detection of the pulse in the art. radialis and, therefore, with the appearance of the first sound it is possible, of course, to determine the blood pressure more accurately with the Riva-Rocci apparatus than through the pulse.

Dr N I Kulbm There was no agreement on the theories. Some are inclined to explain the origin of the sounds differently than Dr Korotkoff. Of course, the subject cannot be considered exhausted. How applicable is your method?

The Speaker I worked with normal vessels. Possibly in pathological cases these sounds are produced by the vessels themselves."

In issues of the same journal in the next year, 1906, under the title of, "On measuring the blood pressure with the sound method of Korotkoff," there are extensive observations by D. O. Krilov²² on the origin

of the Korotkoff sounds From numerous experiments, which are fully described and graphically shown, Krilov concluded that the sounds were produced by the fluctuating or centrifugal movement of the blood particles and the simultaneous vibration of the wall of the vessel In considering the conditions under which these phenomena arose, he discussed but could provide no definite knowledge on the speed of movement of the blood He described all the influences which affect this speed, namely, the passage of the pulse wave, the degree of vessel compression, the rate of flow and the volume of blood passing through the place of constriction, the height of the pulse wave, the pressure in the vessel, the condition of the walls, and the caliber of the vessel and, to some degree, the specific gravity of the blood In view of the different combinations of these factors and the variation in their effects, he considered that they are responsible for the variety of sound phenomena observed All attempts, he stated, to estimate the normal speed of the blood flow were futile, if the Korotkoff method did not permit the measurement of the speed of the blood stream, it had at least made it possible to estimate the fluctuations of this speed, which had diagnostic and prognostic value

The Korotkoff technique became rapidly accepted and gradually widely used Impetus to its widespread use came from the experiments of physiologists, from the actual practice and precepts of able clinicians such as Janeway, from instruction in medical schools, and from the requirements of insurance companies Though considerable study of the last several years has been given to the pathological state of the blood pressure, and though various reports have again been made on the interpretation of the various sounds, especially the diastolic reading, the original remarks of Korotkoff and his colleagues remain tenable, a testimony to the high caliber of their physiological thinking

Clinical sphygmomanometry, now available in general medicine, became the source of two important contributions to medicine It increased gradually the knowledge of the state of the blood pressure in health and disease More importantly, one may believe, it facilitated the general spread of physiological concepts, it helped to develop the appreciation of the historical course of disease by focussing attention on disturbance in function rather than in morphology, and, along with clinical thermometry, it led to more precise and accurate thinking in clinical medicine

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DECEMBER 1941

ARTERIOSCLEROSIS *

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WE have increased the expectancy of life from forty years at birth in 1850 to sixty-three years at the present time. This increase in life expectancy is due largely to the control of infectious diseases of childhood and early adult life. We are an ageing population, among whom chronic non-infectious diseases, notably diseases of the cardiovascular system, are becoming more important. The medical handling of these diseases includes little hope of cure, since a disease is usually well-established at the time of its discovery. The principal promise lies in the direction of prophylaxis. Prevention can be applied most intelligently when we have specific evidence of the cause of a given disease. Concrete evidence in this respect is now available with reference to the most important chronic disease, atherosclerosis.

The term arteriosclerosis is properly limited to non-infectious chronic disease of the arterial system. Arteritis, whether syphilitic, rheumatic, typhoidal or related to other infections, thrombo-angitis obliterans, periarteritis or polyarteritis nodosa and productive thrombotic diseases are excluded.

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We are left with the arteriolar (diffuse) sclerosis, Monckeberg's sclerosis, and atherosclerosis. Arteriolar sclerosis is characterized by (1) hyaline intimal lesions which are analogous to those occurring in atherosclerosis, by (2) hypertrophy and degeneration of the media, by (3) proliferative thickening of the subendothelial layer of the intima, and is closely allied with hypertension.¹ There is also a close relation between hypertension and atherosclerosis, particularly with reference to the coronary arteries.

Monckeberg's sclerosis, responsible for beaded and pipe-stem arteries, is not clinically significant. The media is calcified in the relaxed state resulting in dilatation of the vessels. Clinical disturbances are due to engrafted atherosclerosis.

Atherosclerosis is responsible for most of the arteriosclerosis which is clinically significant. It was named mushy sclerosis literally by Marchand because of the fatty-mushy-material in the lesions. Adam and Aschoff² demonstrated that the fatty material was made up of myelin bodies, later shown to be cholesterol esters. Anitschkow and Chalutow³ produced the disease in rabbits by feeding cholesterol. The experimental evidence was not generally accepted and the experimental disease was referred to, disparagingly, as the cholesterol disease of rabbits. All active human atherosclerotic lesions contain excess cholesterol. Only healed (scarred) or calcified lesions are free from this excess. In other words, active atherosclerosis cannot occur without cholesterol.

Cholesterol is a hydro-aromatic secondary alcohol which can unite with fatty acids to form esters. It is contained in all animal cells in normal amounts, hidden in the cells, and disclosed only on chemical examination. All visible cholesterol is excess cholesterol. Excess cholesterol is present in atherosclerotic lesions in two forms: esters which occur in droplets—the so-called fluid crystals of Lehmann—and solid notched oblong plates. Both fluid and solid crystalline forms are anisotropic (doubly refracting) and permit of identification of the substance in the lesions.

Phagocytic cells pick up excess cholesterol esters, much as they would engulf particulate solid matter. These cells, loaded with fine ester droplets, are known as foam cells. Though other lipoids—kerasin, sphingomyelin—may be found filling foam cells in the rare lipoidoses, 90 per cent at least of foam cells in human tissues carry cholesterol esters.

Cholesterol was looked upon by Starling as the stable substance of

the animal cell, in whose interstices the more labile substances underwent metabolism. With ergosterol it is the only sterol capable of absorption through the intestine. Vegetable sterols are not absorbed. The dietary sources of cholesterol are egg yolk, milk and meat fats. Cholesterol is the source of the sex hormones and adrenal corticosterone, is closely related to the bile acids, the fat soluble vitamins and the carcinogens. Its metabolism appears to be under thyroid control. Females mobilize cholesterol during pregnancy, and appear to possess a better cholesterol metabolism than do males.

Cholesterol is an irritant. It is, however, relatively benign, provoking chronic irritant effects. In this respect it is akin to silica. Gye and Purdy⁴ injected silica sol (colloidal silica) intravenously into rabbits, and produced after long delay a characteristic triad of lesions, cirrhosis of the liver, enlargement of the spleen and changes in the kidney characteristic of chronic "interstitial" nephritis. I have been able to demonstrate that adequate amounts of cholesterol fed to rabbits will produce after long delay, in addition to atherosclerosis, cirrhosis of the liver, enlargement of the spleen and chronic vascular nephritis.⁵ Both silica and excess cholesterol are difficult of metabolism, tend to persist in the tissues for long periods, and stimulate a growth of connective tissue.

THE LESIONS OF ATHEROSCLEROSIS

According to the Virchow-Aschoff theory, the wear and tear on the vessels by pressure of the circulating blood produces a swelling of the deep layers of the intima accompanied by degeneration. The arterial intima is not vascularized but depends for its nutrition on imbibition or diffusion of plasma through its tissues from the blood circulating through the lumen. Cholesterol esters, according to this theory, are precipitated from the plasma in its passage through the swollen intima and occur as free esters in the lesions. These free esters are picked up by phagocytic cells from the intima, which constitute the foam cells found in the lesions.

Klotz⁶ insisted that the earliest lesions of atherosclerosis were marked by the presence of foam cells. There was no swelling or degeneration of the intima, and no free cholesterol esters. He believed that the description of Aschoff applied to advanced lesions. The free esters were due to the disintegration of foam cells as a part of the progress of the lesion.

My studies of early lesions have supported Klotz' findings. The early-

est lesions show foam cells in the subendothelial layer of the intima. There is no swelling or degeneration of the intima, and there are no free esters.

Atheroma In the early youth the stay of foam cells in the subendothelial layer of the arterial intima may be temporary. A mechanism which I have described⁷ removes the excess cholesterol from the lesions and the tissues are restored to the normal. This power to remove excess cholesterol rapidly from the tissues is gradually lost as age comes on but persists in the ascending aorta into old age.

Atherosclerosis Progressive lesions, i e., those of true atherosclerosis, are marked by stimulation of connective tissue growth due to the excess cholesterol in the foam cells in the lesion, invasion by the foam cells of the deeper layers of the intima, necrosis of the deep layers as the lesions enlarge beyond the power of plasma diffusion to support them, vascularization, repair with scarring, or calcification. In very susceptible persons in youth, and as a standard lesion in older ages, foam cells may pile up in masses without adequate provision for nutrition or for physical support of the cells. Massive necrosis of these cells gives rise to lesions with soft mushy contents whose thin covering layer tends to rupture at a touch. These lesions are improperly called atheromatous abscesses. They are actually antitheses of abscesses. There is no cellular exudate and the concentrated cholesterol prevents infection. A better term for such a lesion is atherocheuma (literally mush liquefied). Atherocheumas may rupture producing atheromatous ulcers, which may give rise to thrombi and, rarely, to dissecting aneurysms.

Nodular lesions of the types mentioned above are characteristic of human atherosclerosis. The progressive steps in the evolution of the varied gross lesions of the human aorta can be followed with considerable accuracy.⁷ The response to fat stains and the anisotropic property of the excess cholesterol together with the distinctive appearance and staining reactions of the foam cells make such a study possible.

CORONARY SCLEROSIS

The frequency with which lesions of the coronary arteries occur and the serious character of the lesions are in all probability due to the unusual stresses which these vessels are called upon to bear. The coronary orifices are located just above the aortic ring in a region exposed momentarily to maximum stress by the closure of the aortic cusps. The pressure

is quickly relieved by diffusion through the elastic aorta but must have an influence on the structures subjected to it. Furthermore, the coronary branches are distributed through the muscle bundles of the heart. In experimental animals the ventricular wall can be seen to become pale during systole, due to the compression of the muscular arterial branches, the capillaries and the veins. Meantime the primary coronary vessels and the main subepicardial branches, not subjected to compression, are filled with blood under systolic pressure and cannot be emptied. The principal coronary circulation is during diastole.

Probably because of these unusual stresses, the coronary arteries develop, beginning in the "teens" or earlier, a thickened intima in the form of what I have called a "buffer" layer. Other vessels, notably the proximal portions of the intercostal arteries, the hepatic artery, and the vessels of the penis, uterus and ovaries, subjected to stresses, develop thickened intimas, unrelated to arterial disease as such. But in none of these vessels is the thickening so constant and so perfect a part of the vessel as is true in the coronary arteries.

The localization of the lesions of coronary sclerosis is due to stresses and is most constant in the proximal 3 to 4 cm. of the left coronary artery and its descending branch. Not only are the lesions most constant in this site but they tend in general to progress toward occlusion more rapidly here. The left coronary artery in this region turns almost at a right angle from its origin and gives off almost at a right angle a very large branch, the circumflex. The right coronary artery does not undergo such a change in course and does not give off a large branch so early. However, as atherosclerosis progresses both coronary vessels and many of their branches are affected. In advanced cases the distribution of the lesions may be essentially equal in both coronaries.

Coronary sclerosis furnishes the best evidence that atherosclerosis is not a disease of age. In my series advanced coronary sclerosis at 12 and 15 years of age and coronary deaths at 24, 25, 26, 28, 29 years of age, with many in the thirties, determine that issue beyond question.⁸ Many of the young victims were robust athletic types. There were no stigmata of senility in any of the younger group.

Coronary lesions tend to vary in their histologic makeup with the age of the individual. The initial invasion of the subendothelial layer of the intima by foam cells is followed by stimulation of connective tissue and thickening of the intima. The foam cells invade the deep layers of the

thickened intima New waves of foam cells invade the lesion as it enlarges Necrosis of the deep layers, which are furthest removed from the lumen, is usual If the lesion is to enlarge, a new source of nutrition must be found Capillaries arising in most cases directly from the lumen supply this need In some cases extensions of the vasa vasorum furnish the new circulation In *youth* the capillary system lies in a relatively loose textured connective tissue Rupture of the delicate capillaries may result from compression by coronary spasm (Hall and his associates⁹ have produced coronary occlusion with infarct production, and also coronary thrombosis—without atherosclerosis—by the use of acetylcholine, which provokes coronary spasm) Hemorrhage from capillary rupture is followed by fibrin formation and fibrinoid necrosis This may extend to the lumen and thrombosis may follow Thrombosis is the usual termination of coronary sclerosis in youth

In the *middle period* of life there is a greater tendency to collagen production, and scarring of the lesions is outstanding The new accretions of foam cells are perhaps less frequent than in the group who die early in life Narrowing of the lumen by the encroaching lesion is on the whole slower in this period Hypertension is a common associated condition As the lumen narrows a state of coronary insufficiency may result In a large percentage of members of this group death of coronary type may occur without occlusion of either main coronary artery or of any branch of a size adequate to account for so rapid a death Indeed the individual may undergo an acute coronary seizure, may be hospitalized for days before he dies, and postmortem examination may disclose an infarct with no occlusion of main vessels or of branches supplying the infarcted region Spasm alone can account for such a lesion Rarely one finds in this group a well vascularized coronary lesion with a delicate capillary system, with capillary rupture and thrombosis—the lesion associated normally with younger individuals Calcification of the arteries following necrosis in atherosclerotic lesions is common but scarring is the main characteristic of the lesion in this period

In *older ages* the common lesion is one of atherocheuma formation The reaction of connective tissue to the presence of cholesterol is less marked Enough connective tissue to support the massed lipoid cells may not have been produced Death may result from coronary insufficiency, but frequently death is due to the rupture of an atherocheuma The pasty contents of an aortic atherocheuma are broken up in the whirling

blood stream and can produce at most capillary embolism. The pasty contents of a coronary atherocheuma can cause immediate occlusion of the lumen. Secondary thrombosis can occur when death is delayed. Scars from older lesions are common in old age, as is calcification.

Continuity of heart action is, of course, essential to life. As Lewis has demonstrated, muscular action without adequate oxygen is responsible for pain, and accounts for angina. The oxygen requirements of heart muscle are greater than those of other tissues excepting the brain. As coronary disease narrows the vascular lumen the common cardiac lesion is chronic vascular myocarditis or myocardosis. As the blood supply is cut down the oxygen-demanding muscle fibers undergo atrophy and, if the interference with supply progresses, the fibers disappear. The tougher connective tissue which replaces them proceeds rapidly to scar formation.

At the other end of the scale we have the true infarct due to a sudden cutting off of the blood supply by thrombosis, rupture of an atherocheuma or spasm. In this case we have necrosis not only of the muscle fibers but also of the supporting connective tissue, followed by acute inflammatory exudation.

Midway between these lesions and apparently due to spasm is a process of rapid necrosis of muscle fibers in small regions, but followed by a stimulation of the supporting connective tissue, associated with little or no inflammatory reaction. These lesions have been called *miliary infarcts*. They are not true infarcts. A better term is *miliary myocardoses*.

Rupture through the necrotic tissues of an infarct may cause death by hemopericardium and cardiac tamponade. Rupture of an atherosclerotic coronary artery may lead to hemopericardium. Dissecting aneurysms of the coronary arteries are rare. Infarcts are repaired by granulation, sometimes with pericardial adhesions. The scar tissue repairing an infarct may stretch producing a cardiac aneurysm. Thrombi undergo organization, if the individual lives, sometimes with canalization. Rarely the canalization may reestablish the circulation in considerable part. Usually the blood flow is reestablished about the region of thrombosis by a collateral circulation.

Coronary occlusion (1) may be symptomless, (2) may cause mild or serious illness, or (3) sudden death with ventricular fibrillation, or (4) death so instant as to suggest immediate cerebral arrest with cardiac and respiratory standstill.

EXPERIMENTAL ATHEROSCLEROSIS

Just as the primary stage of human atherosclerosis is marked by the presence of foam cells in the subendothelial layer of the intima, so in the primary stage of experimental atherosclerosis in the rabbit foam cells appear in the subendothelial layer of the intima. This suggested a search for the source of these foam cells.⁵

There is a period of weeks following the beginning of cholesterol feeding in the rabbit before the first lesions appear in the ascending aorta. The reason for this delay—this latent period—was made clear by feeding cholesterol to a large series of animals and killing an animal on every second day in the critical period beginning with the fifth week. In frozen sections of the liver stained with Sudan IV the blood, rich in cholesterol after several weeks' feeding, stained deeply. The fat was limited to the blood. In animals killed later isotropic fat could be seen in the cells in the centers of the liver lobules. Later anisotropic fat appeared in the form of cholesterol esters in central cells, and began to accumulate in the liver cells (see footnote).^{*} In animals allowed to live for longer periods the cholesterol esters accumulated in liver cells until a large part of the cells of the lobule were filled. In these animals the adrenal glands also began to show visible enlargement. As the amount of cholesterol esters in the liver and adrenal cells became greater there came a point at which Kupffer cells in the liver and reticulo-endothelial cells from the capillaries of the adrenals began to remove the excess esters from these organs. The esters were picked up by these cells as though they were particulate matter.

In animals which had received a great excess of cholesterol and had lived well beyond the latent period, the overloading of the liver and adrenal cells with esters reached such a degree that the liver sinusoids and the adrenal capillaries, as also the lymphatics, became blocked with phagocytic cells loaded with cholesterol esters. As a result the procedure of removal of the excess esters was so slowed up that the details of the process could be followed. The cells loaded with esters, now become foam cells, made their way into the lymph and blood stream. They were carried in the circulation to the lungs. They passed through the wide lung capillaries apparently with ease. The so-called filter of the lungs is

^{*} It has been assumed that the liver esterified cholesterol since Thannhauser and Schaber¹⁰ in 1926 demonstrated that in "parenchymatous" liver disease there was a lowering of the ratio of ester to free cholesterol in the blood. We now have optical evidence of liver esterification of cholesterol. Esterification of cholesterol was observed by Chalotow¹¹ in the cells of the adrenal glands in 1922.

efficient for larger masses such as megakaryocytes, but foam cells, ameboid and fitted to make their way through the interstices of solid tissue, found no difficulty in the passage. Having passed the lungs the cells invaded the subendothelial layer of the intima of the aorta. This invasion of the arterial intima must be due to a positive chemotaxis, since cells carrying particulate matter do not tend to invade the aorta or arterial intima. The only exception to this rule is the invasion of the aortic intima by cells carrying polyvinyl alcohol.¹² The chemotaxis and arterial invasion by foam cells may thus be a type reaction, limited to the higher alcohols.

The foam cells which mark the first stage of atherosclerosis in human and experimental lesions have now been brought from origin to destination in the experimental rabbit. It is a reasonable assumption that the mechanism of atherosclerosis production in man is the same as that seen in the experimental animal, though in less dramatic form. The progress of human atherosclerosis is so slow that the formation of foam cells in the liver must be only occasional and perhaps localized within this relatively enormous organ.

The lesions of atherosclerosis in the experimental rabbit duplicate much more exactly human lesions than do the attempts to reproduce in animals the lesions of many human infections by the use of their known causal agents. Such differences as are found between human and rabbit atherosclerotic lesions are dependent largely upon differences in the method of cholesterol feeding—in a single continuous sequence over a period of months in the rabbit—intermittently at intervals over a period of years in man.

Since cholesterol is the cause of atherosclerosis the disease is preventable. There are indications that the human body can synthesize the cholesterol it needs. The substance is apparently required in greatest amount during periods of active cell production. The cholesterol of egg yolk is needed for the embryo. The cholesterol of milk is required by the nursling after its intrauterine supply from the blood of the mother has stopped. At any rate the needs of the body for this substance must be less after the period of rapid cell growth has passed. Prevention by diet should be more successful than is true of diabetes, since cholesterol does not appear to be a necessary part of the diet. Vegetable fats, whose sterols are not absorbed, may be substituted for animal fats.

Choline and lipocain, which are said to prevent the excessive deposit

of fat in the livers of experimental animals, may influence the deposit of excess cholesterol in the arteries. The evidence in that direction up to now is not very strong, however.

SUMMARY

Atherosclerosis, the important form of arteriosclerosis, is distinguished from other forms of arteriosclerosis by the presence of excess cholesterol in the lesions. It is the "cholesterol disease" of man.

Excess cholesterol, i.e., visible cholesterol, is an irritant, producing lesions in the experimental rabbit (in addition to atherosclerosis) resembling those produced by intravenous silica.

Earliest lesions of atherosclerosis in the experimental rabbit and man are marked by the presence of foam cells containing cholesterol esters in the subendothelial layer of the normal arterial intima. This lesion regresses in atheroma by a mechanism of cholesterol removal. It progresses in atherosclerosis to produce the characteristic nodular lesions of the disease.

In the experimental rabbit, fed cholesterol, it has been possible to observe the esterification of cholesterol in the liver and the adrenals, deposition of these esters in liver and adrenal cells to the point of becoming a burden, engulfing of the excess esters and their removal from the liver and adrenals by Kupffer and corresponding cells, escape of these cells into the circulation, their passage of the lungs and invasion of the arterial intima. Thus are begun new atherosclerotic lesions, or accretions are made to those already started.

Excess cholesterol is the cause of atherosclerosis. Stresses determine the localization of lesions. Thyroid secretion controls cholesterol metabolism. Sex, age (time + thyroid deterioration) and heredity are modifying factors.

Diet, with limited or absent cholesterol, should prevent atherosclerosis. Vegetable oils, whose sterols are not absorbed, can be substituted for animal fats.

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CORONARY INSUFFICIENCY OBSERVATIONS ON DIAGNOSIS AND TREATMENT*

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CORONARY insufficiency is a functional disorder, not dependent upon any specific anatomic lesions for its occurrence. It may be defined as that condition in which the coronary arteries deliver less blood than is required for the effective performance of the heart. The disproportion between supply and demand can be brought about by a number of different factors which either diminish coronary flow or increase cardiac work. Its commonest cause is disease of the coronary arteries. Its two most important effects are anoxia and ischemia of the heart muscle. According to the current concept acute, local anoxia is the chief cause of cardiac pain. Prolonged ischemia, in the sense of a permanent reduction in coronary flow, may induce fibrosis of the heart muscle, cardiac hypertrophy and, eventually, congestive failure. In this discussion cardiac infarction and congestive failure will not be considered. Attention will be focussed on the paroxysmal type of pain to which the term "anginal" has been applied.

CAUSES OF CORONARY INSUFFICIENCY

Before proceeding to a consideration of diagnosis and treatment, it is necessary to have clearly in mind the various clinical conditions which may result in an inadequate coronary flow. Among the most important are

- 1 Diseases of the coronary arteries
 - A Atherosclerosis. This may be
 - a Slight, with patchy intimal change and loss of elasticity
 - b Marked, with calcification and narrowing

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- c Occlusive, as a result of obliteration of the lumen by the sclerotic process or due to the formation of a thrombus
 - B Syphilis of the aorta, with stenosis of one coronary orifice, or of both. The specific process is limited to the first 3 or 4 mm. of the coronary arteries
 - C Embolism. This occurs infrequently, the two most common sources of emboli are bacterial vegetations on the mitral or aortic valve, or a thrombus covering a sclerotic plaque at the root of the aorta
 - D Rheumatic fever, with involvement of the coronary arterial walls and, occasionally, thrombus formation
 - E Periarteritis nodosa, a relatively rare condition, but one in which coronary involvement is not uncommon
- 2 Aortic valvular disease. In aortic stenosis, less frequently in aortic insufficiency, the coronary blood flow may be diminished. In free aortic regurgitation this is believed to be due to the lowered diastolic pressure
 - 3 Anemia. The heart suffers from anoxemia along with the rest of the body
 - 4 Paroxysmal tachycardia. The rapid rate may call for a greater coronary flow than can be delivered
 - 5 Hyperthyroidism. The increased metabolic demands of the body require a faster velocity of blood flow and an augmentation of volume output by the heart. Cardiac work may exceed coronary reserve
 - 6 Combined states. For example, a person with coronary sclerosis will experience pain more readily if marked anemia is present than if the oxygen-carrying capacity of the blood is normal. Ischemia and anemia complement one another in causing anoxemia

It is thus evident that pain of coronary origin may result from systemic disorders as well as from those which are primarily cardiac. But there are other conditions which, on occasion, induce pain in the chest, and simulate that due to coronary insufficiency. Among these are

- 1 Acute, serofibrinous pericarditis
- 2 Aneurysm of the thoracic aorta
- 3 Cholelithiasis

- 4 Duodenal ulcer
- 5 Poisoning by coffee, tea or tobacco
- 6 Intercostal neuralgia or myalgia
- 7 Psychoneurotic states

The aim of diagnosis is to determine the etiology, to define the anatomic lesions and to estimate the degree of functional impairment. No attempt will be made here to outline a complete diagnostic survey or to give a full account of therapeutic procedure. These remarks deal with scattered observations, assembled over a period of years and concerned chiefly with cardiac pain due to coronary sclerosis.

DIAGNOSIS

In no other condition is the patient's account of his discomfort of greater importance. Often this suffices for diagnosis. So, it is essential that the physician who is responsible for the management of the case should himself take the history. A story obtained by a colleague, no matter how competent he may be, cannot convey the same impression as that obtained from a personal interview. From this contact is often obtained the key to the entire situation. There is established an understanding and a relationship which is never gained through an intermediary. Furthermore, pain is so frequently the only evidence of coronary disease that its precise description by the sufferer must be heard in order that its significance can be appraised and its implications analyzed.

The physical examination may be entirely negative. The heart is often not enlarged, the sounds are normal and the blood pressure is not elevated. The retinal and peripheral vessels may show no sclerosis. Of positive value, though in no sense etiologically specific, are cardiac enlargement and weak heart sounds. Sometimes the first sound at the apex is split, a diastolic gallop may be heard. The presence of hypertension is not, of itself, a decisive feature.

The same viewpoint obtains with respect to the electrocardiogram. A normal record does not rule out the presence of advanced and, sometimes, serious coronary insufficiency. A case has previously been reported,¹ in which a patient with a typical history of anginal pain presented no objective signs of cardiac disease. The four-lead electrocardiogram showed no characteristic changes in T waves, RS-T segments or in conduction. Yet within twenty-four hours, this man of 49 died suddenly at the breakfast table. The presence of abnormalities in the elec-

trocardiogram is, however, of great help in furnishing positive evidence of myocardial damage

Not infrequently, it is difficult to decide whether a person complaining of pain in the chest is suffering from coronary insufficiency or from one of the conditions simulating it, having its origin either within the thorax or below the diaphragm To aid in differentiation and in detecting latent coronary insufficiency, the "anoxemia test" has been devised and, in our hands, has proved to be of practical value^{2,3}

In principle, this test consists of permitting the patient to breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes, or until cardiac pain appears Measurements of electrocardiograms taken at intervals during this period reveal, in patients with a diminished coronary reserve, characteristic changes which are not observed in the presence of an adequate coronary blood flow A positive test may thus be regarded as a sign of coronary insufficiency, but a negative test does not exclude the presence of disease of the coronary arteries The occurrence of pain during a negative test, that is, one in which no electrocardiographic changes have occurred, affords *presumptive* evidence of a diminished coronary reserve⁴ It is of particular significance when the pain appears during the first 10 minutes of induced anoxemia Patients experiencing painful discomfort during a negative test should be carefully observed for further signs of coronary disease and managed conservatively

The criteria of a positive reaction have been evolved after experience with the performance of the test more than 1100 times in over 500 persons, some with normal hearts, others with cardiac disease They are as follows

- 1 The arithmetical sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm or more
- 2 There is partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm or more, in this lead
- 3 There is complete reversal of the direction of T in Lead IVF, regardless of RS-T deviation
- 4 There is partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm or more, in this lead Of the four, this criterion is of the least value It rarely occurs alone, and has been noted twice in borderline cases⁵ If further experience confirms these observations, it will be discarded

The anoxemia test is simple and safe. Unpleasant reactions have been observed, such as vasovagal attacks, panic, loss of consciousness and dyspnea. These were relatively uncommon and not serious. In the course of 4 years, there has been no evidence of permanent injury to a single patient, although the test has been performed in the same person as often as 20 times. Early in the work, pulmonary edema occurred 3 times. But if the test is not given to a patient with congestive heart failure, to one who has had an attack of cardiac infarction within 4 months or to the same patient twice within 24 hours, no grave accidents are to be anticipated. The percentage of oxygen in the gas mixture should be checked at frequent intervals to be sure that the proper concentration is being supplied.

The test has been helpful in the differential diagnosis of conditions producing pain in the chest. It has been employed to study, in patients, the effect of various drugs on the coronary circulation. It has been useful in following variations in the coronary reserve and so appraising the efficiency of the coronary circulation at the time of its performance.⁴

The following case record serves to illustrate the type of changes which are seen in the electrocardiogram when coronary insufficiency is present, and portrays graphically the increase in coronary reserve coincident with clinical improvement.

Case I W. D., aged 48 years, foreman in a U. S. Post Office, was admitted to the hospital on March 18, 1939. He had been well until a week before, when he had a typical attack of coronary occlusion with cardiac infarction. During this week he had been attended by his own physician. He was transported by ambulance and arrived in good condition.

On admission, the rectal temperature was 100.4° F. The heart was a little enlarged. The rhythm was regular, the rate 64. The first sound at the apex was split. The blood pressure was 120/80. The leukocyte count was 7,880, with 75 per cent polymorphonuclears. The sedimentation rate was 45 mm in one hour, and rose on the following day to 54 mm. The Kline test of the blood was negative. An electrocardiogram showed prolonged auriculoventricular conduction (the P-R interval measured 0.33 sec.). Other changes were characteristic of a posterior infarct.

The patient remained in the hospital for 5 weeks. The course was one of steady improvement, both clinically and in the form of the electrocardiogram. At the end of another 2 weeks (8 weeks after his attack)

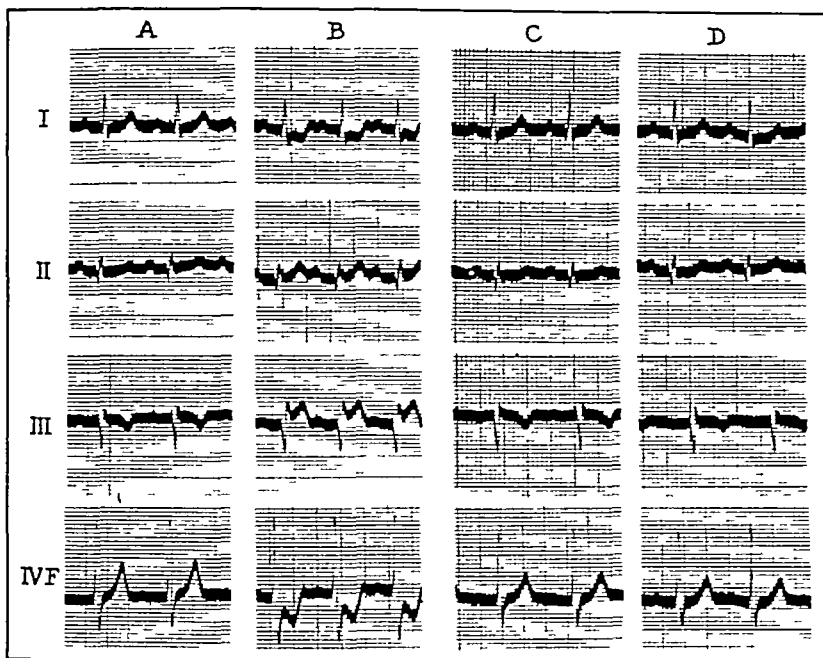


Fig 1 Case 1 W D, male, aged 48 years, foreman in Post Office Coronary occlusion with myocardial infarction on March 11, 1939 Anoxemia test, at first positive, became negative

Five months after attack Working too hard and having frequent attacks of anginal pain A—control B—positive test pain after 18 minutes, total RS-T deviation, 9.5 mm T wave reversal in Leads I and IVF

Nine months after attack Work lighter and nearer home Rare attack no nitroglycerine required C—control D—negative test no pain during 20 minutes of anoxemia

he returned to work, in spite of having been advised to extend his period of rest. When tired, he complained of aching in the left shoulder and arm. Subsequently he experienced cardiac pain on effort and in August, 1939 (5 months after the occlusion) was having frequent anginal attacks. An anoxemia test at this time was positive (Fig 1 A, B).

He was then able to transfer to a Post Office nearer his home and was made a supervisor. The work was lighter and he improved. Nine months after the original attack, he was not taking nitroglycerine and could walk for 6 or 7 blocks before experiencing discomfort. The heart sounds were of good quality. The blood pressure was 120/72. The anoxemia test at this time was negative (Fig 1 C, D).

The test does not furnish evidence which makes it possible to predict the future occurrence of coronary occlusion. Several patients have

suffered such attacks within a few months of the time that a negative test was found. On the other hand, patients with a positive reaction are more likely to have this complication than those in whom the reaction is negative. The test is therefore an index, within undefined limits, of the functional efficiency of the coronary circulation, but it yields no information as to the nature and extent of the pathologic lesions in the heart.

TREATMENT

Medical Measures Any person who has pain in the region of the heart is alarmed. He thinks at once of a relative or friend who has died suddenly following a similar complaint and his first question is apt to be "Have I angina pectoris?" He wants, above all, reassurance. It seems to me good practice, under these circumstances, to state at the outset that there is no disease such as angina, that this term means merely a painful or uncomfortable sensation in the chest, and that it will be our aim to discover the nature of the condition which lies at the basis of the discomfort.

These patients are worthy of the expenditure of much time on the part of the physician and attention to detail is necessary if therapy is to succeed. A carefully planned regimen, designed to save the heart from overwork, will aid in the establishment of a collateral circulation in the coronary bed. The intelligent use of nitroglycerine, not only for the relief of pain when this occurs, but prophylactically, when some necessary effort is anticipated, will prevent the occurrence of myocardial anoxia. There is evidence, both clinical and experimental,^{6, 7} that repeated and prolonged impairment of the coronary blood flow causes minute focal necroses in the heart muscle and, in time, replacement fibrosis. The avoidance of painful attacks is, therefore, of therapeutic importance.

Of the various drugs which have been used in treatment, the xanthines have received most attention. There has been difference of opinion with respect to their efficacy as coronary dilators, and conflicting reports have appeared concerning their usefulness in lessening the frequency and intensity of anginal paroxysms. The changing conditions in the coronary circulation as a result of disease and the many external factors which may modify the clinical course of patients subject to attacks of cardiac pain, make difficult a just appraisal of the effect of medicinal remedies which exert their action over a long period of time.

For this reason, an objective test was applied to the problem in the form of induced anoxemia^{8,9} Changes in the form of the electrocardiogram were studied in patients with coronary sclerosis, before and after the administration of different members of the xanthine group The time of appearance of pain during anoxemia was also observed and variations due to drugs were noted In brief, it was found that various members of the xanthine group (aminophylline, theophylline with sodium acetate and theobromine with sodium acetate) in proper dosage, caused a decrease in the RS-T deviation of the four-lead electrocardiogram and prolonged the time of appearance of pain These results were obtained by averaging the observations obtained in a group of patients and expressing the effects as a trend This was necessary because not all patients respond favorably, as might be anticipated from the varying character of the coronary lesions in different hearts In general, patients with less severe and less frequent attacks show a better therapeutic response than do those with more advanced coronary insufficiency In our hands, aminophylline, because it is best tolerated by the digestive tract and does not require as large doses as some of the other members of the group, has proved the most satisfactory drug It may be given in doses of 0.2 Gm (3 grs) three or four times daily Enteric-coated tablets are available and may be prescribed for those who report digestive disturbances

Recent studies made in our laboratory indicate that the duration of action of this drug, when taken by mouth, lasts only for a few hours This observation suggests that perhaps smaller doses, taken at shorter intervals, might exert a more beneficial action Work designed to indicate the most effective method of administration is now in progress It is our present opinion that in certain cases the xanthines, because they dilate the coronary arteries, bring about symptomatic improvement Whether, if taken for weeks or months, they aid in promoting a collateral circulation, cannot be decided on the basis of the evidence now at hand

Surgical Procedures Most patients with cardiac pain respond favorably, in some degree, to medical therapy But there are those who suffer so intensely that they question the desirability of living Fortunately, they do not form a large group They welcome with enthusiasm any form of therapy which offers a reasonable hope of relief

Of the various operative measures which have been suggested, only one will be considered at this time Cervical sympathectomy and total

removal of the thyroid gland have not stood the test of trial and have been almost universally discarded. Section of the dorsal nerve roots, performed on a few selected cases, has been successful, but it is a major operation requiring laminectomy and presents a real hazard for the patient with advanced coronary disease. The operation for the formation of a new blood supply to the heart, as devised by Beck,^{10,11} holds out real promise, particularly if the technique can be simplified.

There remains for discussion paravertebral block with alcohol. This was first suggested by Swetlow in 1926¹² and has been done in various clinics, both in this country and abroad. The largest series, 62 cases, has been reported by J. C. White of Boston.¹³ My own experience, recently published in collaboration with R. L. Moore, is based on observations in 45 patients.¹⁴ Since our results and those at the Massachusetts General Hospital are comparable and similar, I will confine my comments to the material with which I am familiar.

Alcohol block is a simple technical maneuver, but it requires an operator familiar with the landmarks, skilled in their use and deft because of constant practice. The effectiveness of the injections depends entirely upon the accuracy with which the ganglia and *rami communicantes* are infiltrated. Our results may be summarized as follows:

Of 40 patients subjected to final analysis, 77.5 per cent experienced varying degrees of improvement, no relief was obtained in 22.5 per cent. In 47.5 per cent of the total number benefited, improvement was permanent to the time of the last follow-up examination, which in 2 cases was more than 9 years. In 40 per cent, relief was marked, in 5 per cent it was moderate and in 2.5 per cent it was slight. Temporary relief was obtained in 30 per cent. This was marked in 15 per cent, and moderate in 15 per cent. In short, there is a 75 per cent chance of relief, and if relief is obtained, there is an even chance that it will be permanent. Neither the duration of symptoms nor a previous history of coronary occlusion nor the degree of incapacity prior to injection appeared to influence the outcome. The postoperative appearance of Horner's syndrome was not essential to a successful result.

In none of our cases was relief complete. Even when a result was obtained which was satisfactory to the patient, some form of discomfort persisted, to act as a warning signal. There were sometimes actual twinges of pain, of less intensity than before injection, or a sense of pressure beneath the sternum. In several cases, mild dyspnea or a sinking

sensation in the epigastrium was substituted for pain

Almost invariably (in 38 of 40 patients) painful intercostal neuritis was observed after the injection. This was severe in only 3 instances. It lasted from 2 weeks to 3 months but eventually always disappeared. Whereas it was a cause of complaint, the relief of cardiac pain, when obtained, more than compensated for discomfort. In 5 cases, a small pleural effusion developed which was always absorbed within a week. Pneumothorax, reported by others, was not observed. Increased temperatures, from 99 to 104° F, occurred in 25 patients, fever never lasted more than 4 days unless complicated by pleural effusion. There was no operative mortality.

Why, in some cases, relief should be temporary and in others permanent, has been explained by the recent experimental observations of Merrick.¹⁵ He found that in cats, when a ganglion was infiltrated with alcohol, permanent block was produced to all regions innervated by the postganglionic fibers taking origin from it. This occurred because the alcohol killed the ganglion cells. When the rami communicantes alone were infiltrated, only a temporary block was produced, for regenerating fibers penetrated fairly early through the connective tissue scar formed at the site of injection. Partial block in patients is probably due to incomplete destruction of the ganglion cells or rami.

There is some reason to believe that abolishing or relieving cardiac pain not only affords symptomatic relief but has an effect on the coronary circulation and so on the heart muscle. A group of Toronto investigators,^{16, 17} working with conscious dogs, observed that when the heart was denervated, the mortality following sudden occlusion of a coronary branch was materially less than in the intact animal. These experiments were regarded as indicating that, by preventing afferent impulses from reaching the vasoconstrictor center, reflex spasm of collateral coronary arteries was prevented. It was apparent also that sympathetic denervation rendered the myocardium less susceptible to the onset of ventricular fibrillation. Clinical and necropsy observations support those made in the physiological laboratory.¹⁸ Of 376 patients who died of coronary sclerosis and thrombosis and were examined post mortem at the Presbyterian Hospital, 52 died suddenly. In the group with pain, death was sudden in 27.5 per cent, and in the group without pain in only 9.1 per cent. Regardless of the extent and character of the coronary lesions, the presence of pain tripled the incidence of sudden death.

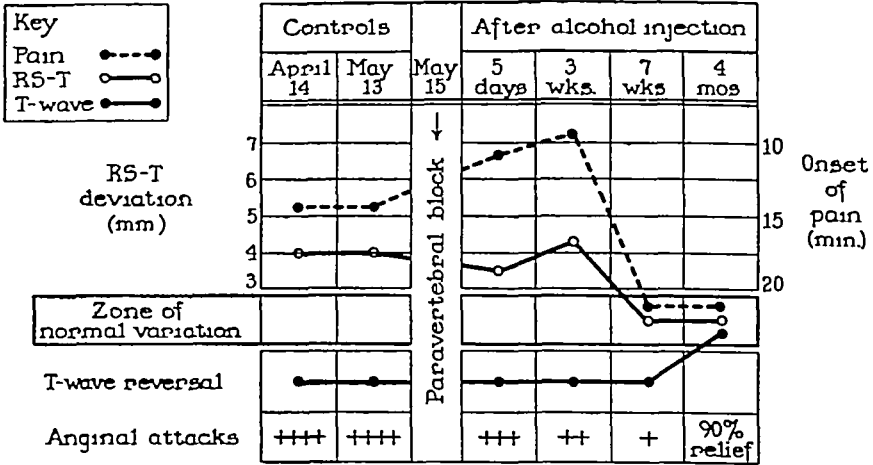


Fig 2 Case 2 O F, male, aged 53 years, automobile salesman Anginal pain for five years, unable to work for the past three because of disability Anoxemia test positive prior to paravertebral alcohol block Four months after injection, coincident with clinical improvement, test became negative.

In 2 of our cases, changes in the form of the electrocardiogram occurred shortly after alcohol block The alterations in the complexes were in the direction of normal and suggested an improvement in the coronary blood flow¹⁴ Observations with the aid of the "anoxemia test," made before and after injection, have shown in the one patient in which this has been done, remarkable improvement in the coronary reserve, coincident with clinical improvement (Fig 2) A brief abstract of the clinical record follows

Case II O F, aged 53 years, a male, automobile salesman, for 5 years had been having typical anginal pains radiating to the left arm Disability became progressively more marked and for the past 3 years he was unable to work He also had a feeling of substernal pressure and dyspnea after meals He was unusually intelligent and cooperative

Examination showed no cardiac enlargement, either on percussion or in the teleroentgenogram The heart sounds were of fair quality There was no gallop, a blowing systolic murmur was heard at the apex The blood pressure was 140/82 The electrocardiogram showed regular sinus rhythm with a Q wave present in leads one and two There was no defect in conduction and the T waves were normal There was no anemia The Kline test of the blood was negative

The anoxemia test, done on a number of occasions, was positive

Two controls, obtained at an interval of a month, were identical (Fig 2) They show the occurrence of pain at the end of 14 minutes, a total RS-T deviation of 4 mm and significant reversal in the direction of the T waves

Paravertebral alcohol block was done on May 15, 1941 by Dr R L Moore Injections were made in the region of the first five dorsal ganglia Horner's syndrome developed There was moderate pain from intercostal neuritis, which disappeared in the course of 2 months At the end of 4 months, he estimated the degree of improvement at 90 per cent He was able to walk 2 or 3 miles without discomfort, except after a heavy meal He had not used nitroglycerin since the operation and stated that dyspnea was gone The blood pressure was 140/80 The form of the control electrocardiogram was unchanged The anoxemia test at this time was negative

In view of these various pieces of evidence, it appears that interruption of the sensory pathways, in certain cases, may diminish or abolish spasm in the coronary bed This is a desirable effect, tending to promote a more adequate collateral flow in unaffected vessels As has been previously suggested, earlier relief of pain in patients with coronary sclerosis might be expected to influence the course of the disease in a favorable manner But in the more advanced cases, even when the result was good, unilateral alcohol block did not prevent the later occurrence of coronary occlusion or of sudden death

In conclusion, I would like to leave with you this thought The patient with recurring cardiac pain suffers usually from a progressive, disabling disease Yet in some cases there is a remarkable and unexpected turn for the better, in others, the increase in the symptoms of coronary insufficiency is gradual and the degree of disability is slight The physician can bring both aid and comfort He is sometimes discouraged when improvement is slow and his therapeutic efforts appear to be ineffectual He will find it helpful, under such circumstances, to keep in mind three master words—resourcefulness, patience and optimism Of these, the most important to both doctor and patient is optimism

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THE PSYCHOPATHOLOGY OF PSYCHOPATHIC PERSONALITIES*

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PSYCHOPATHIC personalities have been described in a variety of ways from the time of Koch¹ in 1893. He and various followers were impressed by the finding that there were many who though not having any specific mental illness were, nevertheless, not to be termed normal in their mental states. It was noted that these individuals had differences in one way or another from the ordinary everyday person—differences which set them somehow apart. Psychiatrists from the first tended to view those deviations as being congenital lacks and they included feeble-mindedness as one of the types as well as hysteria and psychasthenia.

The psychic inferiorities were however subjected to further analysis as a result of which intellectual defects were withdrawn from this group as being a well defined entity which was susceptible of fairly sharp delineation. For the same reason Adolf Meyer² separated neurasthenia, psychasthenia and hysteria from the psychopathic states, preferring to keep the latter designation for a variegated assembly of what he termed "inferiorities not sufficiently differentiated." These he characterized as constitutional psychopathic inferiorities. The fullest descriptive accounts of the clinical pictures of these psychopathic personalities we owe to Grasset³ in his book entitled "The Semi-Insane and the Semi-Responsible," and to Kraepelin⁴ who in 1915 gave the classic delineation of seven types of deviated personalities: the excitable, the unstable, the impulsive, the eccentric, the liars and swindlers, the anti-social and the contentions.

Since that time the importance has been increasingly realized, both for the individual's life adaptation and for that of society in general of the phenomena, the understanding, and the management of such prob-

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lems Their wide range, their great numbers, the complexities involved in attempts to deal adequately with them, have led May⁵ to declare that "the influence of these individuals on the community at large is something we have no means of estimating at the present time," and that there is no greater problem today than the attitude of the state towards the psychopathic criminal White⁶ stated the need for our attaining an understanding of these conditions in order that society may take the viewpoint of intelligent management and treatment rather than continue with a punitive and retaliatory attitude based upon misconceptions of the real nature of the psychopathic states

When we seek to begin a survey of the situation with some clearcut definitions, difficulties at once present themselves As recently as 1921, psychopathy was regarded by some as synonymous with the term insanity Bleuler⁷ has stated that it is but vaguely differentiated, that it deals with "deviations from the normal in all possible directions and mixtures" Kahn⁸ tells us that it is impossible to give an exact definition of the psychopathic personality, so that we cannot say "Psychopathic personalities are—," but must be content to observe, "By psychopathic personalities we understand—" Kurt Schneider's⁹ statement is an admirably restrained one He says, "Psychopathic personalities are those abnormal personalities who suffer from their abnormality or from whose abnormality society suffers"

This places the accent upon the basis of community interest or upon the individual's own reactions to his condition It is our present purpose rather to examine into the actual facts of this interesting mental deviation and to consider some of the details of its psychopathology, to determine whether any closer approximations can be made to a definition or clarification of the mental processes involved

We may then review some of the more familiar symptomatology which clinical observation has amassed While there is a great variety in the actual conduct of psychopaths, there are least nine aspects of their reactions some or all of which are so regularly found as to justify special attention They are the following

- 1 Inability to postpone
- 2 Ineffective consideration of consequences
- 3 Insufficient learning from experience
- 4 Faulty synthesis
- 5 Disproportionate responsiveness

- 6 Affective dominance over intellect
- 7 Devaluation of reality
- 8 Disregard for truth
- 9 Insufficient social valuation

We will proceed to examine these factors. The first was an incapacity for delaying. It may be shown in the symptom of spendthriftiness, wherein one wants things and proceeds immediately to their purchase, if only the needed cash is in his pockets. Or it may appear when one repeatedly loses jobs because he flares up and voices resentment at his boss too outspokenly. The issue here seems to be that the long circuiting characteristic of our more complicated reflex responses has not taken place, the stimulus has led too directly to an outflow in motor behavior. Such individuals cannot sufficiently recognize that a gratification dependent on delays might mean more than a trivial appeasement at the instant. Apparently the craving for some instant satisfaction exerts too much pressure upon the psychopathic individual.

Related to this difficulty is the second one of a failure to give adequate consideration to consequences. An act by itself might seem justified but when we realize what may result from it, that future possibility often acts as an effective deterrent. This faculty of mind serves to bring the future into the realm of present considerations. Not to be able to give due weight to possible consequences means that one has not sufficiently organized the material of the future. In the complexities of modern living it is more necessary than ever before to keep forming incessantly new estimates and forecasts of the probabilities to come as well as they can be seen from the implications of the present. This however the psychopath often does not do. He will, for example, invent the most fabulous lies without stopping to realize how deeply they will inevitably involve him tomorrow. Or he may sign leases, enter into business contracts, execute promissory notes without being impressed by the need to recognize the demands and the means for ultimate fulfillments.

Each individual must make such blunders in the process of learning these needs and developing skills in meeting them. When the forecast indicates that they cannot suitably be met he calls upon the past to be reminded of some better course to follow. The psychopath, however, does not learn effectively from even repeated experiences. If he cannot organize his future, here is an indication of his equal inability to make adequate use of the past. It seems that he is not able to formulate general

principles from the experiences of his living. Their type value is apparently of less significance than their individual instance value. This is a corollary of his tendency to live in the present with overvaluation of the immediate moment. He cannot detach himself sufficiently from his intimate contact with the single items of his living to view them impersonally or objectively enough to derive the rules which they evidence. People with psychopathic personalities not infrequently have a remarkably accurate capacity for critical self evaluation. They are, however, never able to make use of this verbal insight. And their most fervent resolutions for improvement, although eloquently and correctly reasoned, invariably fail.

This is perhaps due to the fourth item under consideration, that of the psychopath's tendency to make incomplete or faulty synthesis. Part of his difficulty in learning the lesson of experience comes from his propensity for dealing with part pictures rather than with the total picture of his situation. The lack of synthesizing ability is probably due to the immediacy in response. The psychopath makes his reaction often to the first portion of a situation which comes to his notice. If the idea of marriage occurs to him, he may propose and be accepted before the financial implications of the marriage have reached his consciousness. Another will make a suicidal attempt because he has just been reprimanded, failing to form any conception of thus receiving training which may help him earn a larger salary. This tendency is readily recognizable in an immature, growing child. It seems in the psychopath, however, to be a more erratic and variable trait, now present, now absent. Like other psychopathic traits it shifts whimsically, being manifested to a differing degree from topic to topic or from one time to another.

A fifth factor equally unpredictable and whimsical is that of unbalanced and changing intensity of emotional response. The customary variabilities of affective coloring show a certain consistency, a roughly similar quantity of affect usually accompanying a given phenomenon. The psychopath, however, seems to have in his bewildering and shifting affectivity a set of emotional values for the items concerned which is quite different from that of the average individual. Thus, the most well-meant bit of teasing may produce a violent rage or a flood of tears, or a word of routine praise may raise one to the skies. A small disappointment can convince a psychopath of the necessity of suicide or a casual remark may suffice to start him zealously upon some previously unconsidered

life vocation. If the emotional accenting within the self is eccentric or disproportionate, likewise its intensity of expression may show gross difficulties of control. "I know it is silly but I cannot help feeling that way," a psychopath will say.

Accordingly it is understandable that the psychopath's intellectual functions may be dominated by his emotional stresses. It seems, indeed, that this is not only true in many instances but that it is a general phenomenon in such persons. It is one of the regularly occurring evidences of immaturity, that the force of emotional argument looms greater than any factual intellectual construction. Wishful thinking is nowhere more in evidence than in this group. One decides that the world owes him a living. He is convinced all evidence to the contrary that he is vastly superior to his fellow men. Never managing to sell one of his productions will not prevent his deep certainty that he is a supreme poet or novelist. We deal here with another approach to several of the factors previously mentioned and indeed all of them are inextricably interrelated. In a given instance it may be impossible to decide which may be causative in producing the other. Such a consideration suggests that there may be some formulation underlying the various factors which might explain their coexistence and their interdependence.

The psychopathic personalities are not psychoses and hence it is not to be expected that reality values of the external world should be actively denied by the psychopath. This is indeed borne out by clinical observations. Reality is not, however, permitted to have its full significance. If he deals with incomplete syntheses not making adequate use of past experience and suffering emotional warpings of his judgment faculties, the psychopath is certainly not making correct, adequate use of reality. He cannot evaluate reality in its true significance when he is aware of it only in fragments. It may therefore be said that it is a trait of the psychopath to devalue reality rather than to deny it. This may be illustrated for example by the fifty-year-old able-bodied man who demands money from his feeble, aged mother "because you are my mother and should therefore support me." The true significance of his circumstances, his actual responsibilities for failures, crimes or disappointments, may all be glibly talked out of existence.

That this might indicate insincerity in one who really knows how the facts stand merely puts the shoe on the other foot, for he then shows a tendency to misrepresent things and evidences a disregard for truth in

its own right. The incontrovertible majesty of the existence of fact remains for most persons quite indisputable. To the psychopath this frequently is not so, as is particularly striking in the case of pathological liars. Their distortion of truth often amazes even themselves and they are at a loss to explain their motivations.

The last point to be itemized lies close to the one just stated, but in our social culture it has attained such preeminent importance as to justify its individual mention. One of the strongest influences on the cultural advance of civilization has been the establishment of such social forces as morals, traditions and precepts, and the formulation of such conceptions as those of duty, reputation, honor and pride. These are psychic processes which are included in the Freudian concept of the superego. To them we owe the increasing effectiveness of management and control of id and ego tendencies. But it is just here that the psychopath is likely to show particular weaknesses and inability to measure up to the customary attitudes of his fellows. The call of duty may be entirely overcome by inherent laziness, the measure of personal pride is often obliterated by the demands of less valued impulses, and reputation, though desired, may not produce enough sustained effort to be attained. Again we face a problem of evaluation in which continuity of influence seems less to the psychopath than to the average individual. A social force is readily overbalanced by a personal inclination. Apparently the cultural values are viewed from behind the psychopath's personal ramparts and are not taken into himself to become part of his own personality, there to cope with other traits in his own makeup.

The result is that the psychopath is more self-centered than the ordinary individual, and that his mental processes appear to behave in a less mature fashion than we expect from the ordinary person. It may be inquired if such traits are inherently different from those of other people, or if they are maladjustments of machinery which if properly tuned should be functioning properly? The importance of such a query is apparent for a rational approach to therapy.

There has not been reported any structural pathology which would offer a somatic or neuropathological foundation for psychopathy. Hence we must consider it as a functional abnormality, a behavioral deviation from what is customary. As soon as that step has been taken, we must seek explanation of the phenomena in terms of dynamics. When we consider a psychopathic personality from this aspect, we have a problem

which calls for analysis of the mental functions themselves. Let us look therefore more in detail at some of those nine types of psychopathic symptoms which have been referred to above.

One was an unsuitable immediacy. Why "unsuitable?" Because our usual ontogenetic development takes us beyond that level of reactivity, so that it represents a functional deviation from the group, a sort of deficiency. We assume that an individual confronted simultaneously with various issues will ordinarily delay action, that is, he will delay in adopting a finally decisive response pattern until, through the processes of association, he has found the most effective compromise he can. This resultant indicates the relative importance he recognizes, according to his own personal experience, in each of the issues he thinks are involved. From his methods of response we can infer, if the various issues are known, a good deal about the proportionate weight he feels each issue carries.

The indecision of a psychasthenic keeps him for hours from selecting between two neckties, and we consider this an evidence that values are quite evenly balanced. The psychopath's undue speed in settling his decisions approaches the other extreme at which one factor is not only given preference, but exclusive or preponderating preferment when other issues should have their real values also under consideration. If certain details preempt his attention, others can exert only a lesser claim upon the psychopath for his consideration. It is not our present purpose to determine any ultimate reason for this but merely to call to attention that it does occur in psychopathic reactions. This makes it appear that one factor in the psychopathic phenomenology may be an overvaluation of certain material so that it acquires an improper ascendancy over other items. It would not matter what the overvalued items were but rather that some overvaluation had resulted in a corresponding undervaluation of other material so that the response lacked in validity, in adequacy, in accuracy, or, we may say, in general acceptability.

If others of the psychopathic qualities mentioned are examined, it will be seen that they too contain this same difficulty. When the psychopath fails to take due heed for consequences, he is living in the present or near future without seeing the somewhat more distant future as clearly, without granting to eventualities as much importance, as others do. In other words the meaning or interest of the present is still as it was with all of us in childhood, more vivid and more real than is that of a dim,

vague future. Once more we see that certain items are still holding first place in the psychopath's mental functioning which should have made allowance for the coexistence and the significance of other items. That these latter seem vague, or less significant, is but another way of saying that one's accented attention remains still upon the former items. This is to say, that lack of diffusion of interest has caused a continuing fixation which is inadequate because it takes into account too limited a portion of reality.

It is the same with the classical incapacity of the psychopath to learn some of the vital lessons even through repeated experiences which contain the material that might teach him. It is a common clinical observation that, although he may be able to state in glib exactness all sorts of precepts and maxims which are logically derivable from his experiences and those of others, the psychopath seems not to be actually touched by the meanings inherent in his words. Even though his intellect has worked out the answers, they have not acquired enough comparative affective weight to claim parity with his overly egocentric notions. If one cannot be influenced by the book he will not read, no more can he evidence deep-rooted effects from his own experiences if he has not bestowed sufficient attention upon them to make them glow with a personal, meaningful value. "Yes, quite true," he will say, "but what does that mean to me? Nothing."

The other types of psychopathic symptomatology can be viewed from the same standpoint. The devaluation of reality, for example, is something quite different from a mere honest difference of opinion as to the significance of facts, just as it is inherently different from psychopathic denial or delusional distortion of reality. What the psychopath does with portions of reality is to have their meaningfulness to himself as emotionally colored stimuli differ from what it is to the average individual. Hence the power of reality to move the psychopath, to arouse him, to teach him, to limit him, is not what it is to others. It may well be that some factor within himself is functioning in a way to lessen the meaning of outer reality to the psychopath, and this by the mechanism of no active inhibition or repression but through the more placid phenomena of mere limitation of the attention to details of more interest to him.

Perhaps we may learn from the popular social attitude which so often pronounces accusingly about some dereliction. "If you cared enough

to have thought about it, you would have realized" Evidently the psychopath does not "care enough" about many of the items and the issues which have considerable meaning for most of us And as he obviously has no disinterest, but rather too intense an emotionality, it would seem in line with clinical facts that his interests are simply centered elsewhere

The majority of individuals, through experience and training, develop a certain degree of social-mindedness in which their sense of values is largely predicated upon social consciousness, their decisions are modified by regarding themselves as an inherent part of the group Their affects and behavior are thought of as modifying and as being modified by those of others, and hence are regarded by those individuals as requiring frequent checkups so as to be kept, like one's watch, set correctly with others The psychopath on the other hand has to those individuals something of the same comparison as had the Ptolemaic theory to the more advanced Copernican theory of the universe To the psychopath he himself is the center of the universe about which everything else circles In his essentially narcissistic viewpoint, whatever is outside of the focal point, himself, is tacitly excluded, it is not absorbed as being a part of his own self His boundaries are quite personally limited From the social approach this means that he lacks in that social identification which would properly articulate his inner self with his associates From the standpoint of personal psychology his concerns seem to have been fixated upon pure self interests which characterize mere egocentricity

It must be asked If the psychopath is a narcissist, if he is so absorbed with the fascination of his own inner drives to the detriment of the usual wide derivatives which lead others to augmented horizons and to broadened, socially controlled interests in life, then, how is his state different from that of dementia praecox, which is likewise termed a narcissistic state² A distinction can be drawn as follows Dementia praecox produces actual distortions of outer reality, as by believing the hospital nurse to be one's deceased grandfather Psychopathic personalities do not make such a distortion of factual realities, but they have a personal set of values for external realities so that to them those realities hold different implications, leading to non-usual associations or behavior Thus, a schizophrenic planning his day's work may be interrupted by hearing God's voice, but the psychopath, by being so intrigued with a discussion of poetry that the conceptions of duty, punctuality reputa-

tion and personal pride in achievement confront him with comparatively lesser urgency

The psychopath is susceptible to the push of externally applied motivation, but often seems not to have enough energy available to motivate himself from within in the way we say he should. But if the pressure implicit in the words "should" or "obligation" or "expected" which come to an individual from outside were withdrawn, he would be left with only the impulses from his inner self. These, if considered at an early period in life, are utterly egocentric, they make use of externals for personal gratification alone. So it seems to be with the psychopath, who to varying degrees regards the world of people and situations about him, not so much in their own right as existing entities themselves, but rather in relation to their potential adequacy for gratifying his own immediate wishes.

Here we return to a factor referred to above. The psychopath seems to have a responsive tendency which is uneven, perhaps explosive, at any rate often disproportionate. This is because we judge of reactions in their relationship to the outer world of reality. We expect similar settings of the external picture to call for similar graduations of an individual's inner responsiveness. When the external situation is, say, seven o'clock, and Monday morning, and job duty in one hour's time, our regard for the pressure of the external facts makes us get out of bed. But if one's mental associations are restricted to the planning of a party for that night, the pressure towards arising will be markedly decreased. Such an inner primacy of wish-phantasy-urges is the dominant factor in the psychopathic personality. That is why his responses may seem out of adequate proportion. His inmost balances of affectivity and the instinct drive-urges of the moment are what determine the outflow of his energies, rather than the stage setting in which he finds himself and by which standard we are accustomed to measure his adequacy.

To sum up, it is the view here set forth that in psychopathic personalities there is to be found as a definitive characteristic a certain fixation or limitation in psychic development. This consists of a continuing restriction of affective attachments such that significance or urgent motivating value does not widen its scope to include as much of the world of reality external to the self as is usual in adult life. It is a permanence of some attitudes of human psychology which were normal for one level of the evolving mental complexity, but whose continuance is indica-

tive of a form of persisting immaturity. It is an enduring tendency to measure by a personal rather than by a social or group yardstick, but involving no further distortion of reality.

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THE INFLUENCE OF CLIMATE AND GEOGRAPHY ON HEALTH*

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IT is with deep appreciation of the honor conferred upon me in being asked to deliver this Lecture that I speak tonight. Particularly appropriate is it that the title of the lecture suggested by your Committee on Public Health Relations specified the influence of climate and geography on *health* and not on *disease*. Factors controlling health and well-being are always more important, because the greater part of any population mass is composed of people who are in good health and who wish to remain in that favorable state. Analysis and elucidation of these factors underlying maintenance of health, however, are greatly facilitated by close scrutiny of conditions predisposing to disease. In the presentation tonight I shall therefore set forth a picture of climatic and geographic dominance over health much more extensive in its ramifications and implications than is generally considered, but much of this picture will be based upon the study of climatic and geographic variations in certain types of disease. The geographic factor will be disregarded except as climatic characteristics vary from one region to another. Certain transmissible diseases show a geographic influence quite divorced from climatic effects, dependent more upon density of population, urbanization, industrialization, freedom of travel and intercourse, and upon a variety of other such factors not to be considered in the presentation tonight. For the sake of clarity and emphasis, attention will now be directed almost exclusively to the climatic factors affecting the maintenance of health.

In considering these climatic factors it is necessary to look upon man (and other warm-blooded animals) as an energy conversion machine—a machine that operates only by virtue of the energy it derives from the

* The Hermann M. Biggs Memorial Lecture delivered before The New York Academy of Medicine at the Stated Meeting, April 4, 1941. Illustrations used at the time of delivery have been omitted from the text here published. Most of them may be found in the author's book "Medical Climatology," published by Charles C. Thomas, Springfield, Illinois, 1939.

cellular combustion of foodstuffs. An individual is alive only so long as this combustion continues, and the level of his vitality seems determined by the intensity of his tissue fires. He is not an efficient energy-conversion machine, however, being able to utilize for work performance only 20-25 per cent of his total combustion energy. This level of working efficiency is about the same as that of a good gasoline motor, but is far below the 37 per cent efficiency obtained from Diesel engines. Other warm-blooded animals (horse, dog) exhibit this same 20-25 per cent level of working efficiency.

The human body in action is therefore faced constantly with the necessity of dissipating into its surroundings the remaining 75-80 per cent of its combustion energy as waste heat. It must be able to dissipate this heat readily, for any heat accumulation means fever and severe disturbance of body functions. The human body is much more sensitive to over-heating than is any inanimate motor and so has developed an intricate and complicated heat loss mechanism involving vasomotor control of blood supply to the skin and activity of the sweat glands. This heat-loss mechanism operates efficiently to take care of the short-term loads that go with periods of bodily activity or sudden difficulty in heat loss brought about by a rise in external temperatures. It is not necessary to consider here the operating details of this heat-loss mechanism beyond saying that its adaptability is truly remarkable and its capacity great indeed.

When the body is faced with prolonged difficulty in getting rid of its waste heat, however, it tends to bank its tissue fires and reduce the load upon this delicate heat loss mechanism. Difficulty in heat loss continuing for only a few days results in little or no adaptive change of combustion rate, but, if it persists for 10 days to 2 weeks or more, then there occurs a definite slowing down of cellular combustion and a more sluggish pace of life. The belief has for some time prevailed in American medical circles that man shows no such seasonal response to changing temperature level (this is discussed in a separate article, *Amer Jour Hyg*, May 1939, 29, 147-164). Careful review of the literature and the evidence available, however, indicates clearly that men do indeed show this responsiveness to change in external temperature level. This is an important point, for the general vitality and existence level of individuals now seem determined by tissue combustion level and any factors altering the tissue combustion level at once assume great importance in

life The major effects of climate upon human existence become more easily understood when we view them against this background of climatic dominance over ease of body heat loss

Difficulty in the dissipation of the body's waste heat, prolonged beyond two weeks, results in a slowing down of tissue combustion, and with this goes slower growth, retarded development, reduced fertility, lessened resistance to infection, and lowered energy for thought or action Under conditions where optimal ease of heat loss prevails on the other hand, growth is most rapid, development of sex functions occurs earliest, fertility is highest, ability to produce immune bodies and to resist infection greatest, and energy most abundant for the support of an active existence Body form is distinctly more rotund in stimulating coolness and general vitality higher by every measurable index

Human growth in tropical warmth is retarded just as is that of experimental animals, while in middle temperate latitudes it proceeds most lustily During a very recent stay in Panama the author had an opportunity to study height-weight data on Canal Zone school children, and to see what effect varying periods of residence in the tropics have had upon their growth The Canal Zone offers a most valuable opportunity to study climatic effects divorced from those of tropical disease and faulty diet Zone sanitation is on as high a level as that of the most progressive northern cities, while the bulk of the food is imported from the United States Meats sold in the "gold" commissaries are imported from the United States or Argentina American children of any age, born on the Isthmus, are considerably taller and heavier than are native Panamanians, but those born in the Zone are inferior in stature to those newly arriving from the United States during the recent influx for new lock construction

Most significant is it, however, that the stature of those children born in the United States was found to deteriorate more and more with each additional year of residence in the Zone Here is almost pure evidence of climate working alone, evidence pointing to the same depressing effects of tropical warmth as were observed in experimental animals

A sharp lowering of human reproductivity takes place during seasons of depressive moist heat at southern latitudes or during seasons of exhausting cold in the north Human fertility rises highest in any locality when mean monthly temperatures are around 65° F, and is depressed when winter temperatures fall below 40° F or those of summer

rise above 70° F Human conception rates may be suppressed as much as 50 per cent by severe summer heat waves that are prolonged beyond a duration of two weeks

The onset of menstrual cycles in girls also shows the same retardation in tropical heat that is shown by sexual development in experimental animals Menarche comes later in tropical girls, and not earlier as is so universally believed by both medical and lay persons of all countries The widespread belief in early tropical maturity is found expressed in medical literature back through the centuries to the time of Hippocrates in Early Greece, but always unsupported by any statistics that may be available It is a belief that may well have been handed down through several thousands of years since the time when even present middle temperate regions had polar climates and optimal conditions for man existed only in what are now subtropical lands Certainly at present girls mature earliest in stimulating middle temperate lands, with the menses beginning 1 to 2 years later in either depressing tropical warmth or exhausting polar cold

The onset of fertility is also delayed most in those regions where the menses begin latest Although sexual intercourse goes on quite uninhibited in tropical warmth, illegitimate first births come at practically the same maternal age as do the legitimate Among people of middle temperate climates, on the other hand, illegitimate first births come at much earlier maternal ages All phases of development are thus accelerated in cool regions—the menses begin earlier, fertility comes on sooner, and the period of adolescent sterility is shorter than in tropical warmth (see *Human Biology*, 1936, 8, 607, and 1937, 9, 43)

In ability to resist infectious invasion and to produce immune bodies against invading organisms, men and animals are again found more highly vital when proper ease of body heat loss permits them to maintain an active tissue combustion Depressing moist warmth (for even as short a period as 3 weeks) produces a sharp reduction in the ability of white mice to survive inoculation with a virulent pneumococcus organism Even though mice be healthy and on a completely adequate diet, those adapted to a 90-91° F environment are practically all dead from a pneumococcic inoculation before those at 65° F begin to succumb Production of immune bodies after vaccine administration has been found much more active at 65° F than at 90-91° F, both for pneumococcus vaccine in mice and for typhoid vaccine in rabbits

Certain human infectious diseases show this same relationship between survival rate and ease of body heat loss. Among some 3100 tuberculosis deaths of indigent patients in a large sanatorium near Cincinnati it was found that those patients born in Cincinnati or farther northward survived the ravages of the disease twice as long as did those born in states bordering the Gulf of Mexico. Actual survival times, from first symptom to death, were 22.7 months for northern-born whites and 11.8 for the southern-born, 16.8 for northern-born negroes and only 9 months for those who had migrated up from the Gulf states. Among European migrants, the survival time was 20.6 months for those from Western and North Central Europe but only 11.7 months for those coming to Cincinnati from Mediterranean countries. Acute appendicitis also shows a markedly higher fatality rate per 100 attacks in the south than in more invigorating northern latitudes. Nor does the more favorable prognosis in the north necessarily reflect better surgical skill or more competent care than is available in the south, for Boston's fatality rate is higher than is that of less favored cities in the upper plains states or provinces. Acute nephritis is another acute infectious disease showing highest death rates in tropical or subtropical warmth and lowest in middle temperate coolness.

In general it is infectious disease that kills off people in the tropics, while in cooler temperate regions death comes more from diseases of degeneration and metabolic breakdown (arteriosclerosis and heart failure, cancer, diabetes, etc.). Laboratory animals kept free from infectious hazards in a warm environment live much longer than do those forced into a more rapid pace of life by stimulating coolness. But the average life span of man in the tropics is shorter, rather than longer, because of the lowered resistance to infection and the greater prevalence of pathogenic organisms.

In certain regions of the earth climatic stimulation rises high and drives man impetuously forward into a highly vital and energized existence. In the broad expanses of tropical lowlands, however, man is held down close to a vegetative level by the difficulty he must always face in getting rid of the waste heat that would be generated by a more active life. Year after year and for centuries without end tropical man is smothered under this blanket of moist heat that saps his vitality and keeps him in a low estate. The racial importance of this climatic depression takes on sharper emphasis when it is realized that over half of the

earth's human population lives under this severe physical handicap. Only in a few favored regions of the earth are climatic conditions such that man can expand and reach the full flower of his developmental possibilities. We here in North America enjoy one of the largest and best endowed of these energizing regions. Southern Australia, New Zealand, and West Central Europe are almost as well favored. Certain limited plateau areas within the tropics are lifted out of the tropical depression by virtue of the altitude factor.

Energizing climates are not unmixed blessings, however, for man does not seem to possess unlimited ability to respond safely to increasing climatic stimulation. In the most stimulating climates of the earth he is showing alarming evidences of bodily and mental breakdown from the fast pace of life. These evidences of stress are most severe in those parts of the body economy most intimately concerned in the combustion processes. Perhaps 85 per cent of the energy used in living is derived from cellular combustion of glucose. It is not surprising, therefore, that breakdown in the body's ability to mobilize and prepare this sugar for cellular use should occur most frequently in populations living where tissue combustion is most active. Diabetes mellitus represents just such a breakdown in the body's ability to transform the food eaten into the special form of glucose needed for cellular combustion. Diabetic death rates rise highest in urban populations across middle temperate latitudes of America, but there is also a ten-fold rise in colored rural death rates from the disease from Gulf states northward to Michigan and New York. Diabetes exists in tropical countries, but largely as a non-troublesome glycosuria with little tendency for the development of acidosis or coma. In more stimulating climates, however, the disease is severe and the dangers of acidosis and coma very real.

Another way in which the stress of too energizing a climate is manifested is in exhaustion of the body tissues producing the red blood cells. Only in the most stimulating climates does pernicious anemia assume troublesome proportions. Its death rate rises highest in those same middle temperate latitudes of America where diabetes death rates are highest. Death rates for toxic goiter, leukemia and Addison's disease show similar climatic relationships.

Most striking, however, is the close relationship heart failure shows to climatic stimulation and ease of body heat loss. Classification of vascular and heart failure deaths is still too confused and lacking in unifor-

mity from one part of the country to another for valid regional comparisons to be made. Seasonal swings in mean temperature level in a given region, however, bring just as marked changes in tissue combustion rate and load on the heart for oxygen transportation as do regional climatic differences. There has been shown a marked inverse relationship between heart failure admissions to the Cincinnati General Hospital and mean monthly temperatures throughout the year (dealing only with those heart failures not precipitated or complicated with acute infectious attacks or other direct precipitating events). These non-infectious heart failures are about four times as frequent in winter cold as in summer warmth. During certain Cincinnati winters when warm, balmy weather largely prevailed (1929-30, 1930-31, 1931-32) this type of heart failure dropped almost to the low summer level of frequency. This exemplifies clearly the changes in heart load and circulatory stress that accompany environmental variations in the ease of body heat loss. Circulatory load and blood pressures rise with winter cold and fall during summer warmth. Vascular spasm may add considerably to the circulatory embarrassment of winter weather.

There now seems little doubt that one of the chief factors activating or depressing human existence is mean temperature level and the ease with which body heat can be lost. With the active combustion of a cool region goes a higher vitality and more vigorous development along all lines. Even mental processes show this activation, for intelligence or aptitude tests given college students result in markedly lower ratings with tests given during summer heat. But certain hazards attend too active a pace of life, and it is this type of degenerative and breakdown disease which is now causing chief concern in the earth's most stimulating regions.

A second climatic factor, with effects upon human health quite different from those of mean temperature level, is cyclonic storminess. Sudden storm changes in the weather seem largely responsible for the timing and initiation of many types of infectious disease, particularly those of respiratory and rheumatic types. There occurs a marked increase in disability from respiratory infections among employed workers during winter storminess. Rheumatic fever attacks show a similar seasonal variation in frequency.

Temperate zone storminess is largely determined by the passage of alternating major "high" and "low" areas across a given region, bring-

ing marked and often abrupt changes in temperature, barometric pressure, wind velocity and precipitation. Each storm area produces pressure and temperature changes for hundreds of miles on each side of its center as it moves across the continent, so that people living in the great central trough of North America must face almost constant weather change during the winter season. In summer the storms are reduced in number and follow a more northerly course, leaving the South then under a blanket of almost undisturbed tropical moist heat. The Southwest (New Mexico, Arizona, and Southern California) is the only part of the United States unaffected by cyclonic storminess, and that is the region to which chronic sufferers from respiratory and rheumatic infections should go for refuge.

During certain years of unseasonable warmth winter storminess is greatly lessened, with almost as much of a reduction from normal as the summer decline from the winter level. During warmer and less stormy years respiratory disease frequency drops and the general health of the population shows marked improvement. Death and sickness rates rise during the colder, more stormy years. In the southern hemisphere, storm changes tend to be more evenly distributed throughout the year or even to be somewhat greater in summer than in winter. Thus winter existence down there does not carry the sharp increase in health hazards people face in north temperate lands where winter cold and the season of greatest storminess coincide.

Little information is yet available as to just how weather changes affect man. Simultaneous occurrence of changes in the several weather factors makes it difficult to unravel and study the separate effects of each factor. Some of the effects of sudden temperature change and body chilling or overheating are known, and some hints have been found that storm changes in barometric pressure may produce profound disturbance in body functions through alterations in the tissue water balance. However, the matter needs thorough study under controlled laboratory conditions where each factor can be investigated separately. Lack of laboratory facilities for such study has left us with only vague and fragmentary information as to just what effects weather changes do produce in the body. Findings of great health value will probably result when such an investigation can be properly carried out. It seems likely that sudden weather change will be found a potent factor in the *initiation* of many types of acute infectious attacks (particularly respira-

tory and rheumatic infections), but that *ability to survive* the infection depends more upon prevailing mean temperature levels and ease of body heat loss. Thus man has less respiratory infection in summer warmth, not because of a higher vitality during that season, but because of reduced storminess. Actually his ability to fight infectious invasion is sharply reduced in severe summer heat.

Let us now consider climatic effects in still another light, again involving the cellular combustion processes that furnish us the energy upon which we live. This time the vitamins are involved, particularly the B fractions, each of which now seems to act as a catalyst at a given stage of the glucose combustion. Intake requirements for thiamin and other members of the B complex have been found to be fairly constant in man and other mammalian forms under normal conditions. But if cellular combustion is slowed down by external warmth, then the vitamin required for handling each gram of food rises sharply. Twice as much thiamin per gram of food is needed by animals living in a 90° F environment than by those kept at 65° F. Foods with vitamin contents that are entirely adequate in a cool environment become sharply deficient in depressing moist warmth.

This has been clearly shown for thiamin requirements in rats. Food consumption and growth rate at 65° F are almost as good at 0.6 milligrams of thiamin per kilo of food as at any higher level, while at 90-91° F twice this level is required for optimal response. At 65° F real inadequacy is present at 0.2 and 0.4 milligrams per kilo of food, while at 90-91° F even 0.8 milligrams is clearly suboptimal. Preliminary studies have indicated that just as sharp differences will be found for pantothenic acid requirements and perhaps for pyridoxine. Others of the B fractions have not yet been investigated in this fashion.

Recent preliminary studies in Panama have convinced the author that this higher vitamin requirement in external warmth constitutes a severe handicap for people living in tropical heat. Not only are their B requirements higher because of the difficulty in heat loss and more sluggish metabolism, but tropically produced foods seem much more deficient in the B vitamins than are those of middle temperate regions. Meat animals grow much more slowly in the tropics, and their flesh is itself deficient in the B fractions. Eggs and milk products are also deficient unless the hens and cows are fed on vitamin-rich imported foods. It takes about 5 years in the tropics to produce a 1000-pound

ing marked and often abrupt changes in temperature, barometric pressure, wind velocity and precipitation. Each storm area produces pressure and temperature changes for hundreds of miles on each side of its center as it moves across the continent, so that people living in the great central trough of North America must face almost constant weather change during the winter season. In summer the storms are reduced in number and follow a more northerly course, leaving the South then under a blanket of almost undisturbed tropical moist heat. The Southwest (New Mexico, Arizona, and Southern California) is the only part of the United States unaffected by cyclonic storminess, and that is the region to which chronic sufferers from respiratory and rheumatic infections should go for refuge.

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somnia, increased irritability, severe headache, rapid pulse, tremor, weakness and collapse. Recovery followed promptly after cessation of thiamin intake. After a week's rest, thiamin administration was renewed at 5 milligrams daily, and the same toxic syndrome recurred after 4½ weeks at this intake level. Recovery was again prompt after cessation of thiamin intake. While studying the thiamin status of people in Panama during February and March of 1941, the author saw many further evidences of severe toxicity in patients taking 10 to 50 milligrams daily as a more or less routine treatment to obviate the tropical let-down so commonly seen in migrants from cooler climates. The toxicity symptoms were similar to those of hyperthyroidism: insomnia, increased nervousness, hyperirritability, emotional instability, rapid pulse, palpitation, and in many cases nausea and vomiting. Prompt subsidence of symptoms followed cessation of thiamin administration.

Since returning to Cincinnati, the author has obtained evidence of even more severe toxicity, with collapse, syncope, circulatory shock and near approach to death.* These severe reactions have taken place at thiamin dosages of 20 to 50 milligrams continued for two weeks or more. It seems likely that many such severe reactions, and those of a milder character, will be reported now that attention has been drawn to the form such toxic response may take. Better control of thiamin dosage by excretion studies seems badly needed, in order that patients may have the benefit of as much of the vitamin as they really can use, but without being subjected to the hazards of unnecessarily high dosages.

It is possible that toxic reactions to thiamin occur more freely in people suffering from multiple B-fraction deficiencies, as suggested by Morgan in a recent issue of *Science* (1941, 93, 261) and that this accounts for the prevalence of toxic reactions in the tropics where multiple deficiencies seem more prone to occur. The matter needs careful study at an early date if widespread occurrence of ill effects are to be obviated.

The finding of thiamin toxicity has no bearing upon recent steps being taken to fortify white flour or other foods with the vitamins they have lost in processing. No evidence exists to show that thiamin in normal physiologic amounts can be in any way harmful or toxic. Plans for fortification of foods entail only replacement of vitamins previously lost in processing procedures. The finding of definite toxicity from overdosage with thiamin does, however, necessitate a more cautious

* One death from thiamin injection has just been reported to me (May, 1941)

and conservative attitude from both medical profession and laity toward uncontrolled intake of these useful vitamin preparations as they become so freely available

Health assumes then a much more dynamic and buoyant quality in the cooler regions of the earth where body heat can be easily dissipated. Even the vitamin content and quality of foods grown in such regions favor a more active and highly vital existence. In regions of moist warmth, on the other hand, man faces various types of handicaps. He must live at a slower pace because of difficulty in dissipating the larger amount of waste heat that would be entailed by a more active existence. His efficiency seems further lowered by a widespread dietary deficiency for the B vitamins in his foods coupled with a higher intake need. This broad view of climatic dominance over the dynamics of human existence offers a most useful basis from which to attempt an explanation of how climatic environment affects man's health and general welfare. Man is not a standard being of fixed characteristics, but is rather an energy conversion machine highly responsive to the physical and chemical influences affecting his ability to burn food and produce the energy whereby he lives.

Such a dynamic view of human existence at once opens up new possibilities in seeking a better adaptation of population masses to their environment and living conditions. It gives also a clearer insight into the human variations so evident in different climatic regions of the earth, pointing out the factors that hold man back in one land and push him irresistibly onward into an active existence under more favorable conditions. It explains the sharp variations in rate of body breakdown so evident over the earth, and affords at least a partial explanation as to why infectious diseases claim such a high toll in tropical moist heat. It should prove useful in future studies directed toward the better adaptation of man to his existence problems.

THE DOCTOR IN COURT*

PHILIP J. McCook

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YOU have listened to a physician and a lawyer on the subject of "The Doctor in Court." As the Judge honored by the invitation to represent the court in this discussion, I am bound to see the problem of each, indeed, if unable to do so, I cannot understand the problem of the litigant and the public either.

I have assumed the Association desires us to present, collectively, each from his own viewpoint, a picture of cases, mainly of trauma, which call for medical testimony. The general title of the symposium is "Some Medico-Legal Aspects of Personal Injury Actions and Actions for Total and Permanent Disability Insurance." But I have been told that it will be satisfactory if I confine my own remarks tonight to the personal injury actions.

In my court, the form in which these are passed upon is mainly that of cases to recover damages. The Trial Clerk of New York County tells me that, as of June 30, 1940, which I consider a fair and representative date, being just before the summer recess, the trial calendar of the Supreme Court carried 5,257 cases, of which approximately 3,904 or about 76 $\frac{1}{3}$ per cent, were so-called negligence suits. Allowing a little for shrinkage from various causes, it may be assumed that 75 per cent of our Law (as contrasted with Equity) cases relate to personal injuries and are likely to call for medical testimony. Further inquiry leads me to believe that one would not find the proportion very different in the Supreme Court for the other four counties of this City, or in our other civil tribunals, that is, the City and Municipal Courts.

The trial lawyer, naturally and properly, sees the function of the doctor one way, and the medical witness sees it in another. The judge, physically and officially overlooking both, and occupying a detached public position, has an excellent chance to study the viewpoint of each, which he must grasp if he is to understand why they react as they do,

* Address delivered February 25, 1941 in the symposium conducted by the Association of the Bar of the City of New York in connection with The New York Academy of Medicine and the Medical Society of the County of New York.

and whether he agrees with either or disagrees with both

It would be strange, indeed, were the doctor and the lawyer to see eye to eye. One is a scientist, the other, an agent. The former is criticized if he permits himself to become an advocate, the latter, if he permits himself to forget he is an advocate. Yet the doctor, once he has taken the stand on behalf of a party, is scarcely human if he feels no interest in the outcome. This is true even of a subpoenaed attending physician—how much more, of the retained expert. This doctor, employed by one side only, is perhaps in graver and more subtle danger of moral lapse than his legal brother. The barrister, of course, knows that winning for his employer is the best road to professional success, and professional ethics permit and encourage him to follow it. How far the legal profession has at times gone in this direction Lord Brougham is quoted as stating

“An advocate—by the sacred duty of his connection with his client—knows in the discharge of that office but one person in the world—that client—and none other. To serve that client by all *expedient* means, to protect that client *at all hazards and costs to all others* (even the party already injured), and amongst others to himself, is the highest and most unquestioned of duties.”

The author whom I cite for this statement agrees, to be sure, that the great Brougham went too far, saying

“The sum of the whole matter is, that there is no code of morality applicable especially to any profession or avocation (Harris, *Hints on Advocacy* [1881], p. 157).”

The medical witness, in addition to the natural bias springing from association with one side only, is not without selfish motive if retained as an expert. He knows he would never have been called were not his views considered favorable to his employer. Yet he is not permitted, by the ethics of his profession, to seek that employer's success. Putting it differently, the doctor, being a witness, is sworn to tell the truth, and when properly questioned must tell the whole truth. The lawyer on the other hand, being an agent only, but also a responsible officer of the court, is not in normal circumstances required to bring out the whole truth by his questions.

Summing the whole matter up again, the lawyer is always an advocate, while the doctor is false to his oath if he becomes an advocate.

From this anomaly stem many misunderstandings and recriminations.

The lawyer is jocularly regarded as a man hired to defeat the ends of justice by delay and the suppression of evidence, the expert sneered at as one who sells evidence and covers his hypocrisy with large language. Yet, I am sure, a great majority of our doctors and lawyers alike desire, above all, to serve justice and truth, and would never dream of deliberate suppression of an important fact.

The explanation is that our system is one of necessary antagonism between conflicting interests, where each side is represented by an advocate required to call fact witnesses, and sometimes other witnesses, supposedly favorable to his side. How the need for expert testimony originally arose and was met has been often and adequately considered, and I shall not attempt to compete with historical articles like that of Learned Hand, written in 1901 (*Historical and Practical Considerations Requiring Expert Testimony*, *Harvard Law Review*, Vol. 15, No. 1, p. 40), already discussed by Doctor Heyd.

Judge Hand, treating the subject without special regard to medical evidence, proposed at that time a board of experts, or a single expert, to advise on the general propositions applicable to the case, though he refrained from working out the constitution of such a tribunal. He did not propose to prevent either side from calling experts of their own, with every chance for hypothetical questions and cross-examination. "Only," (he says) "the difference will be that the final statement of what was true would be from the assisting tribunal." He evidently believed that when the assisting tribunal had spoken, there would be, and could be, little doubt where the truth lay.

In 1935, Doctors Elliott and Spillman, of New York City, suggested, in "Medical Testimony in Personal Injury Cases" (2 *Law and Contemporary Problems*, p. 466), a mixed tribunal of legal, medical and lay judges, rather than the jury of twelve, of whom the physician would have the function of deciding questions as to the "causal relationship between the defendant's act and the injury for which plaintiff seeks damages and as to the extent and permanency of the injuries thus caused." That was quoted in support of a plan said to be essentially similar, by former Chief Judge Crane of our Court of Appeals, in a 1932 address before the Association of the Bar, published in the *New York Law Journal* of January 29 of that year. All that I can find, however, which Judge Crane said on the subject appears at the end of subsection "V," to the following effect:

“What a speedy disposition there would then be of all these automobile accident cases when the court could appoint arbiters without limit—a lawyer, a doctor, a layman—who would dispose of the cases satisfactorily, yes, more satisfactorily than most of the courts and juries”

The authors, as the title of their paper indicates, are thinking of criticisms of medical testimony in personal injury cases

In 1936 a report to the California Bar Association, Volume 10, California State Bar Journal, at page 183, after considering the various suggestions for improvement in the practice with relation to the subject, including panels of experts, observed that the latter might be subject to political influence in their organizations and so exclude the best qualified, who, though reluctant generally to testify, “if called on by the court in an individual case, would readily respond” The same year Justice Steinbrink (6 Brooklyn Law Review, p 155) reached the conclusion (which I understand is the one likely again to be proposed by the commission of which Mr Kernan is the head) that it is advisable to have a law passed giving the court power to appoint an expert of his own choosing—“a disinterested, competent and licensed physician”—and to tax his compensation as costs (Report of the State of New York Law Revision Commission for 1936) In view of Mr Kernan’s presence here, and what I understand is his intention to discuss the subject, I add only that whatever experience I have had as a judge leads me to the conclusion that it would be unwise, even if possible, to deprive the parties of the right to call their own selected witnesses, including experts

I have myself on proper occasion, though cautiously, employed the practice of asking the parties in open court to let me name a supplementary or assisting expert So far, I have never met with refusal, and, as it happens, I have also been able in every case to arrange satisfactorily the matter of my expert’s compensation The experiment has worked well, however, I realize that such uniform good fortune is not likely to continue, and I cannot see any serious objection to having what I am at present able to do only on consent, given the sanction of a statutory power bestowed upon the court

Dr Heyd has commented on the practical dangers and difficulties of the expert panel idea Of course, he knows much more about that subject than I If such panel, or panels, were to be established by agreement, between responsible medical associations in this city, I am sure that I, for one, would be glad to consider any name on the list, when

indicated, either on consent of the parties, or under statutory powers not now possessed by the justices of my court

I must venture, however, to differ with him in his doubts whether the judge should be allowed to call his own expert. The only reason he gives against it is, that the doctor most intimate and confidentially close to the judge would probably be his family physician, who may or may not be a medical expert. I confess I would be apt to turn primarily to my family physician for advice where I should go, if I did not already know, to find a general practitioner or specialist suited to my purpose. I submit that if I am to name an expert, as I have been doing on consent, and would like to be able to do as matter of right, I should not be hampered in my choice. Influenced I may be, and must be, by personal considerations, such as the confidence I feel for this, that, and the other physician whom I know personally or by reputation. I suggest that this is no objection, but, on the contrary, a recommendation.

However, before we leave this subject of an expert chosen by the court, I freely state I have found that the conclusions of every doctor I named, like the "assisting tribunal" of Judge Hand, were adopted by the jury, and it is only in case of doubt, where the jury is likely to be confused if an impartial expert is not brought in, that I have ever taken the course of asking consent to such procedure. "If this be treason, make the most of it."

With this confession, that I personally believe no other reform suggested offers great theoretical or practical promise, I pass to the consideration of existing evils, agreeing fully that courts and lawyers cannot permit them to continue unchallenged, but must resolutely seek to eradicate them.

That some of these evils are of long standing, and therefore hard to eradicate, is evidenced by my approval of a list supplied in 1909 by the report to the New York State Bar Association of the Committee on the Regulation of the Introduction of Medical Expert Testimony (32 Report New York State Bar Association, p. 367).

(1) Unsatisfactory standards of experience, inviting charlatanism, (2) partisan, conflicting and hence unreliable character of evidence, (3) loss of time and money, (4) confusing effect on juries of conflicting opinions, (5) unscrupulous hiring by the bar of unprincipled, self-styled "experts", (6) receipt by trial judges of testimony of incompetent so-called "medical experts." Judge Steinbrink, *supra*, adds (7) contingent

fees to experts, (8) unequal consequences to rich and poor litigants, (9) the hypothetical question requirement

Permit me to take them up, one by one, in the light of my own experience

Expertness is a relative matter The possibilities of getting the most expert are necessarily limited by considerations such as the financial means of the litigant and the willingness of the best men to testify Under our New York law, the trial court has full discretion to determine the qualifications of an expert (*Slovovitch v Orient Mutual Insurance Company*, 108 N Y, 56 See also 2 Wigmore on Evidence, section 561) Until he finds a witness qualified, he has the power to exclude his opinions altogether A judge naturally hesitates, however, to deprive a litigant of evidence which the latter needs, slight though its value may be for example, that of a young and inexperienced attending physician, who nevertheless, by reason of required modern training and intelligence is able to furnish some kind of an opinion The jury is always told in that event, and probably should be told in every case, that such testimony is only advisory Indeed, as you know, the jury may reject any expert's testimony if they like (though not capriciously) which constitutes a further and final protection

The partisan character of expert testimony is inseparable from our present system, as I have already shown, and I do not regard it as a fatal objection If too obvious in the case of a particular witness, partisanship defeats itself If present in one side, it will probably also appear on the other, and the jury is quick to size up the situation I certainly agree with the famous saying in 1856 of Lord Chief Justice Campbell, in *Rex v Palmer*, quoted in *Hist Crim Law of England* (1883) Vol III p 389

"It is, in my opinion, indispensable to the administration of justice, that a witness should not be turned into an advocate, nor an advocate into a witness"

He meant, no doubt, that wise and honest barristers and physicians, with the help of the court and the jury, could and would cooperate to that end Such also is my hope—and more than a pious one

No doubt expert testimony does prolong trials, but good evidence is worth taking time for, and what we are trying to work out is the problem of getting good evidence In the old days, hypothetical questions were terrible time-wasters My observation is that this particular

evil is already passing. The rules of form are not so strictly observed by lawyers or required by judges, and courts are quicker than formerly to interfere and cut through to the heart of the matter with questions or suggestions of their own, before the situation becomes acute. I may admit frankly that hypothetical questions bothered me greatly in my earlier days on the Bench, but many years have passed since such a question has caused serious difficulty in any case which I have tried. No doubt my associates would say the same thing.

It is also true that juries are occasionally confused by expert testimony, contradictory in character. I have already explained how I deal with such conditions myself. As a rule, the jury will see through the fog, separate the wheat from the chaff, and either reject the whole thing (as they have the right to do), or pick and choose, which is equally their right. I am often comforted by the reflection—which seems to have occurred to Doctor Heyd also—that perhaps medical expert testimony as contrasted with medical fact testimony is not really quite as important as the experts themselves believe.

It is true that an unscrupulous doctor will always find an unscrupulous lawyer to hire him. Every profession has its parasites. Delousing is a tedious and unpleasant process, which neither your profession nor mine can escape.

I do not like to let pass unchallenged the very serious charge of unequal consequences to the rich and poor. I have already hinted that this is a consideration, how important I do not venture to say. From the same source already quoted, I have it that in 67 per cent of the personal injuries cases on the June, 1940, calendar of my court, the defendant is represented by an insurance company. It is common knowledge that in the majority of all cases the defendant has greater resources than the plaintiff. This is always present (perhaps more often than proper) in the minds of court and jury alike. The judge has many an opportunity to meet the difficulty, and if the law favored by Mr. Kernan's Committee is passed, he will be able to act oftener. I do not know whence the opposition to that law in the past came, but whether it was from the plaintiffs' or the defendants' side, I venture to suggest that a policy which would continue to oppose is short-sighted. Inequality is an unescapable fact, and not confined to cases where expert witnesses are used, it runs right through every system of law, and, indeed, every other system. The wise and the just must be watchful and must be astute.

at every turn, to minimize it

I think I have mentioned, directly or indirectly, all the abuses on this particular list, except contingent fees. An expert witness is often asked by opposing counsel whether his compensation depends on the result. I have no way of knowing how often that in fact is the basis of the expert's retainer. The matter seems primarily the affair of the medical profession. We lawyers have troubles of our own along that line.

So far I have spoken mainly of the expert medical witness, because the discussion seemed to take that turn. The attending physician is the man who plays by far the more important role. To the ordinary litigant in a personal injury trial, opinion evidence, as I have pointed out, may be a luxury, fact evidence is a necessity. Consider a laborer who has broken his leg in an accident and lost two months' wages. No matter how rank the negligence which caused his injury, he will not win unless the doctor who attended him appears in court to testify. On the other hand, maybe the injury has been feigned and a hospital intern knows that fact. If he is not brought to the stand, imposition on an innocent defendant results. Probably the majority of subpoenas in New York County, served on doctors, go to men like that, men whose presence is absolutely essential to a just outcome. Now, since a case in the Supreme Court of this County takes one and a half years to reach, what happens? Almost invariably the doctor has long since forgotten all about the case. To respond means loss of time and money, yet respond he must. He is nearly always exasperated, and sometimes defiant. Nobody can blame him for that.

I can remember when there seemed to be a standing feud between certain trial lawyers and the practicing physicians of this town, over such a situation—one group inconsiderately subpoenaing right and left, naming without alternative a certain day and hour, the other evading or even ignoring service. I am sure matters are better now. At all events, there is not a judge on my bench who would not, if properly approached, require trial counsel to show a medical witness every consideration. If, for example, the latter promises to come when called, he will not be disturbed until actually needed. More than that, the judge will always, when possible, permit his testimony to be taken out of turn, as a matter of additional convenience.

I hesitate to tell any practitioner his duties but perhaps I may be permitted to quote what Dr. J. W. Courtney said to a graduating class

of medical students, in 1915 (*Medical Testimony in Personal Injury Cases*, *supra*)

"The present mode of procedure in our courts, in so far as medical testimony is concerned, is not a particularly edifying one. To illustrate this point, let us take, for example, a case of the type which is most commonly met with in everyday work of the courts—an action of tort for personal injuries. In such a case the plaintiff is practically always of the proletariat class, the defendant, a public service corporation or an insurance company. The army of witnesses on either side is generally appalling. Of these the medical ones alone concern us. They are of two hostile camps, and prepared to attempt, under solemn oath, to uphold opinions diametrically opposed, yet supposedly derived from a single series of facts and observations.

"The situation is a deplorable one, and nobody discerns the glaring wrong of it all with clearer vision than certain high-minded men from our ranks, who have long striven to procure legislative enactment looking toward the abolition of this evil.

"To me, for many reasons which I cannot here enumerate, it seems hopeless to expect that legislative appeal on the part of such men will ever be fruitful of the desired results. Hence it is the bounden duty of every man in the profession so to shape his conduct toward cases which promise to eventuate into court proceedings, that due respect will be given his opinion, that he will not merit the biting sarcasm, the sneers, the raillery and general brow-beating of opposing counsel. And, most of all, that through his efforts the ends of justice will really be accomplished."

Dr. Courtney is dead, but his words, spoken so long ago, still live and merit our careful attention—doctors, lawyers and judges alike. While he was speaking principally of experts, what he said applies in large part to the medical fact witness as well, and is broad enough to include the duty of the latter while he is attending a patient who has suffered an accident and therefore is likely to call him to court some day.

To illustrate from one of my own cases. A plaintiff blamed serious injuries on the defendant's carelessness in drawing off the water from a public pool in which he had dived. His medical evidence aroused my suspicion. The doctor, who certified he had attended the plaintiff, was very vague as to the exact date, and he had no original records with

him—merely notes from such records I adjourned the trial to await his return the next day. He appeared with records which showed conclusively that this patient had been treated by him long before the date of the alleged accident.

I hope the doctors present grasp the seriousness of such an incident. Of course, the jury found for the defendant in a few minutes. Then I had the unpleasant duty of holding a miserable, irresponsible and, as he turned out to be, an habitually drunken plaintiff for the grand jury, which indicted him for his flagrant perjury, and he was sent to prison. The doctor escaped any punishment except whatever humiliation he endured in court, and, I regret to say, he may have been too thick-skinned to feel much of that. Yet it is plain he, like plaintiff's lawyer, had neglected his duty. Each thereby lowered, in open court, the dignity and standing of his own profession.

They had done one service to me, in uncovering what appeared to be a general fault of private practitioners of medicine—neglect in keeping adequate original records, and failure as matter of routine, perhaps because of the scanty nature of their records, to bring whatever they have to court. I am well aware what excuses may be offered, but from the judge's standpoint they are inadequate, and reflection on your part will show we are right.

Next to the complaint that the lawyers and judges waste their time, I hear most frequently that we permit doctors to be imposed upon by compelling them, through the receipt of no more than a subpoena fee, to testify as expert witnesses. Indeed, Dr. Heyd has told you that they are subject to "chiseling" by the plaintiff's lawyer, which indicates his belief that this is a general practice. He states that in New York a physician may not be called upon to give opinions, or to exercise the function of an expert witness, without compensation or agreement for compensation. My own practice has been to regard any such attempt as an abuse of the subpoena, and when appealed to I have generally sustained the witness in his refusal to act as an expert unless reassured. Sometimes, indeed, I have gone so far as to interfere without such appeal (*People v Ruiz*, 211 App Div [2d], 446 at 461-2).

I have tried to examine the criticisms in which we are particularly interested, and discuss them frankly. The medical profession has a just grievance wherever its members are treated discourteously or unfairly in court, which is indefensible. I hope I have explained some of your

difficulties and allayed some feelings of suspicion

Your Committee, gentlemen of the Bar Association, have performed an act professionally graceful and socially useful in inviting us to meet in this symposium to discuss problems of common interest To you, representatives of the medical profession and your several learned societies, I owe thanks for the opportunity of exchanging ideas on a subject which affects the courts so deeply

Yearly, monthly, weekly, wise words issue from the rostrum of the Medical Association and the Bar Association all over the United States The citizen sighs with impatience as he reads about these proceedings in the next day's paper, for the same sheet brings news of dirty work at the cross-roads which the speeches of the pundits may have let pass, perhaps with perfunctory condemnation We cannot afford to ignore this popular criticism, to which honest lawyers and doctors, anxious of course to make a living, but even more anxious to obtain and deserve public commendation, are extremely sensitive Imagine, if you can, the influence on legislation and public opinion of such a multitude, if it could be exercised in unity, armed with the minimum of self-interest and the maximum of interest in the public welfare

We both tend to pontificate, lawyer and doctor alike It is in our blood When the priest announced "Thus saith the Lord," he proclaimed laws of Divine origin, physical, social and moral, with little distinction, at first, among them Thus were born the necessity and opportunity for the lawyer and doctor, with their priestly origin and their priestly responsibilities You think, I know, that through our supposed power with the three branches of government, we lawyers have the final say, even in matters within your province Alas, neither of us seems to have much power left nowadays, and it may be that ere long none will be left unless we have all, by that time, become public officials ourselves So let us continue, while we may, to take counsel together, as equals

In fact, you have the edge You are the doctor, the learned one, which is the meaning of your title When institutions of learning wish to honor a lawyer, they call him "Doctor of Laws" You are, through man's infirmities, the master of masters, and you have declared yourself, in your Hippocratic oath, the servant of servants It is you who rule at the death bed, where we all arrive at the last—you and the priest We turn to you because your knowledge makes you stronger than we, and

because your principles compel you to attend us even when the lawyer no longer finds anything to interest him Continue to be merciful

You have your oath, we have canons of ethics, of which William Travers Jerome once said, in my hearing, that there never was a problem of legal ethics which a child could not settle in a moment once you take the dollars and cents out of it There is more than a little truth in that Maybe we must read your regulations also in the light of human frailties

Doctors, and not lawyers, are the final judges of medical ethics Each of you carries about, within him, his own best informed and severest critic Do not lean too heavily on codes and canons They may afford satisfaction to the mercenary individual seeking an alibi and looking for loopholes They supply cold comfort to the conscientious

Gibran, poet and prophet, said

"He who wears his morality but as his best garment, were better naked

The wind and the snow will tear no holes in his skin

And he who defines his conduct by ethics imprisons his song-bird in a cage

The freest song comes not through bars and wires "

The important thing is that somebody should set an example to the rest of us in maintenance of ideals, kindness to the afflicted, enlightenment of viewpoint, avoidance of prejudice, and most of all, courage in action I do not seek to minimize the disappointment, weariness and self-sacrifice entailed But having carried the torch through the Dark Ages and being, as your representative has admitted to-day, in a better economic position to meet emergencies than we lawyers, you are not likely to falter now that you have in so large a measure the public ear and the confidence of the courts

THE FOUNDING OF THE NEW YORK LARYNGOLOGICAL SOCIETY

SOLOMON R. KAGAN

AMERICAN medical men have been pioneers both in scientific and organizing medicine. As Welch said, "American medicine became independent and took a lead in various aspects of medical sciences." A significant achievement of New York pioneer work may be considered the foundation of the New York Laryngological Society on October 13, 1873. Clinton Wagner of New York City, a foremost surgeon, who studied laryngology two years abroad, foresaw a great future for this specialty. In 1873 he instituted the Metropolitan Throat Hospital in New York City. This was the first institution in the United States which treated exclusively diseases of the nose and throat. In October of the same year he brought together a group of physicians who held positions in throat clinics in New York City for the purpose of organizing a society "not only for mutual improvement and the advancement and enlargement of their limited knowledge of the subject, but for the purpose of establishing on a solid footing with the medical profession at large the specialties of rhinology and laryngology in this country." At this meeting the New York Laryngological Society was established by the following doctors: Clinton Wagner, Frank H. Bosworth, Geo. M. Lefferts, Morris J. Asch, Woolsey Johnson, Horatio Bridge, Charles McBurney, Robert F. Weir, Matthew D. Mann and Francis P. Kinnicutt. Robert F. Weir was elected president, Clinton Wagner, vice-president, and Woolsey Johnson, secretary. Other original resident members of this Society were Andrew H. Smith, Frederick A. Burrall, Beverly Robinson, and Samuel B. St. John, Jr.

Among these organizers were well-known surgeons who contributed important work to their specialty. Thus, M. J. Asch invented the "Asch operation" for a deviated septum, F. H. Bosworth, author of a classical book on laryngology (1881), placed laryngology on a firm scientific basis, G. M. Lefferts, in collaboration with J. Solis-Cohen, L. Elsberg and Knight, founded the *Archives of Laryngology* in New York in

1880 The activities of the Society were manifold. It stimulated research work in a new field of medicine. Rare cases of interest were presented at its meetings for examination and discussion. Discoveries of new theories and treatments, inventions of useful instruments and new methods and ideas pertaining to laryngology were reported and widely discussed and clarified. Dr. Bosworth had read sections of his work, *Nose and Throat*, before the members of the Society who expressed their criticism and opinions. Sir Morell Mackenzie of London read before this Society his paper "Hemorrhage after Tonsillotomy."

The New York Laryngological Society was the first society of laryngologists in the world, and served as a stimulus to the profession for the advancement of medical specialism. Five years later, Frank Davis of Chicago proposed the foundation of a National Society of Laryngologists. It was founded on June 3, 1878, in Buffalo, New York, known as the American Laryngological Association, which also was the first national association of laryngology in the world. Dr. Wagner's idea spread abroad, and fifteen years after the foundation of the New York Laryngological Society, Sir Morell Mackenzie founded in London the British Laryngological Association (1888). Dr. Mackenzie was the first man in England to put specialization on a sound scientific footing and founded the first special hospital, the Golden Square Throat, Nose and Ear, in London.

The difficulty of the foundation of the Society was greatly due to the fact that many physicians of that time looked askance at all specialties. In England at that time specialism was rather frowned upon by the orthodox leaders of the profession. In America this antagonism was markedly expressed by many practitioners who barred the specialists as not being honest and reliable practitioners. In connection with this, it is of interest to tell the fact that some members of the Academy of Natural Sciences of Philadelphia declared that the eminent laryngologist Jacob Solis-Cohen of Philadelphia was engaged in unethical practice. When Solis-Cohen was in the amphitheatre during a surgical clinic at the Jefferson Medical College, the distinguished surgeon, Samuel D. Gross introduced him to the class as a man fast leaving the ranks of legitimate practice to become engaged in a narrow specialty. "Why," Gross said, "he devotes most of his time to a cubic inch of the human anatomy. Some day I suppose, we will have specialists confining themselves to diseases of the nail."

Wagner's pioneer work was therefore of particular value, as he was among the forerunners of the development of specialism in this country. For over ten years the Society was in existence and accomplished much. As the older members, the organizers of the Society, died, the progress of the Society ceased. The last important meeting took place at the home of the last President of the Society, Rufus P. Lincoln, in 1883. He failed to call the usual annual meeting for the election of officers, and while retaining his position as president he died. In 1885, at the suggestion of Abraham Jacobi, the Society was merged with the Laryngological Section of The New York Academy of Medicine.

The Book of Minutes of the Society which contained a complete history of all the work of the New York Laryngological Society was lost at the home of the last President of the Society. I have in possession three letters written by the secretary and two organizers of the Society. These letters throw some light on this pioneer Society and contain a list of its original members.

On February 7, 1874, Morris J. Asch wrote to Jacob Solis-Cohen of Philadelphia:

"You know perhaps from Dr. Robinson that we have formed a Laryngological Society—of which I will write you more fully in a few days. Today I want to know from you if it would be agreeable to you to be elected a corresponding member and let me know so that I can have you elected at the monthly meeting on Thursday next. Otherwise I may have to wait a couple of months perhaps. Anyhow, if I do not hear from you I will propose you. Where can I find the best authority on Naso Pharyngeal Catarrh?"

Many thanks for your kindness to Robinson. The throat hospital is in full blast. In a few days I will write you all about it. Today I am in great haste—and stopped in here so as to be sure to have my letter go."

In the same year the secretary of the Society, Woolsey Johnson, sent the following note to Solis-Cohen:

"230 West 43d—St

New York, Mch 15, 74

J. Solis Cohen, M.D.

Dear Doctor

I have the honor to inform you that at a regular meeting of the New York Laryngological Society, held on the 12th inst., you were elected an honorary member.

The Society is an association of professed Laryngoscopists resident in this city, and meets on the 2d Thursday of every month for the purpose of "promoting the study of affections of the larynx, pharynx and adjacent parts"

The number of honorary members is by the constitution of the Soc limited to ten

Hoping that you will accept the membership thus offered, and that you will be able frequently to be present at our meetings, I am, Doctor, with assurances of my own high regard,

Very respectfully, your obt svt

Woolsey Johnson, Secretary"

Four years later, Dr Bosworth, one of the organizers of the Society, wrote to Solis-Cohen

"26 West Forty-Sixth Street

Friday, Oct 4th-'78

Dear Doctor

I have just learned that the next meeting of the N Y Laryngological Soc is called at my house on Oct 10th, and also that there is a prospect of your being present—I need not tell you what a genuine pleasure it will be to all of us to meet you at one of our gatherings, and I trust that nothing may interfere with your coming

It occurred to me to write to you and ask that you will suggest to me anyone that you would care to meet, and I will only be too glad to extend to him an invitation to be present at the meeting

Our society has been fairly prosperous since its organization and we have done some good things I hope Still I should look for a new interest and enthusiasm to be infused into it, by the presence of one who has done so much in the country for Larvngoscopy—and should like to make your coming the occasion of awakening a something better of individual interest on the part of our members

The meeting is given up generally to the consideration of clinical cases presented, rather than to the reading of formal papers and for next week there is no special work laid out I need not say that we should be glad to listen to anything that you might bring with you—

With regards

Very truly

F H Bosworth"

Short was the life of the New York Laryngological Society, but its accomplishments were significant. It opened a new path in medicine, creating an organization for the advancement of laryngology. It contributed to the introduction of novel ideas, clarification of problems pertaining to this specialty and popularization of new laryngological methods and inventions discovered here and abroad. Many scientific papers were read and thoroughly discussed by able men at the meetings of the Society. The latter served as a valuable ring in the chain of organized medicine.

New York City was the birthplace of laryngology. Horace Green of New York, the father of laryngology, was the founder of laryngology in the United States, and the New York Laryngological Society was the first laryngological society in any part of the world.

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NOTICE

IDENTIFICATION OF INDIVIDUALS IN GROUP PHOTOGRAPHS

The Librarian invites the assistance of Fellows of the Academy in establishing the identity of individuals in a number of old photographs of groups of medical men

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

OCTOBER 2—*The New York Academy of Medicine* Executive Session—a] Reading of the Minutes, b] Introduction of Amendment to By-Laws ¶ Papers of the evening—a] Memorial to Dr Frederick Banting, Charles H Best, Director, Department of Physiology, and Banting and Best Department of Medical Research, University of Toronto, b] The use of insulin in its various forms in the treatment of diabetes, Elliott P Joslin, Medical Director, George F Baker Clinic, New England Deaconess Hospital, Boston, c] Prevention of diabetes from the experimental viewpoint, Charles H Best

OCTOBER 30—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The First Harvey Lecture, "Nervous Activity and Visual Mechanisms," H Keffer Hartline, Assistant Professor of Biophysics, Johnson Research Foundation, University of Pennsylvania

SECTION MEETINGS

OCTOBER 3—*Surgery* Reading of the minutes ¶ Presentation of cases—a] Cases illustrating first paper of the evening, Henry H Kessler (by invitation), b] Cases illustrating second paper of the evening, A G Fuller (by invitation) ¶ Papers of the evening—a] Amputations of the upper extremity (motion picture), Henry H Kessler (by invitation), b] Amputations of the lower extremity, A G Fuller (by invitation), c] Use of local refrigeration in extremity surgery, Lyman Weeks Crossman (by invitation), Frederick M Allen ¶ General discussion ¶ Executive session

OCTOBER 7—*Dermatology and Syphilology*

¶ Presentation of cases—miscellaneous.
¶ General discussion ¶ Executive session

OCTOBER 7—*Combined Meetings, Section of Neurology and Psychiatry and the New York Neurological Society* Reading of the minutes ¶ Papers of the evening—a] Presidential Address, A A Brill, b] The electrofit in the treatment of mental disease, David J Impastato (by invitation), Renato Almansí (by invitation), Discussion by S Bernard Wortis, c] Psychiatric disorders in forty men teachers, Edward B Allen (by invitation), Discussion by Edwin J Doty (by invitation), Emil Altman

Pediatrics—Because of the annual meeting of the American Academy of Pediatrics in Boston the October meeting of the Section was not held

OCTOBER 26—*Obstetrics and Gynecology* Executive Session—a] Reading of the minutes, b] Program presented by the Obstetrical Department of the Bronx Hospital ¶ Presentation of cases—a] Gestation neuronitis, A C Posner (by invitation), Discussion by Harry Aronow, b] Pregnancy after prolonged sterility, change of life, M Rosensohn, c] Central placenta praevia—hyperthyroidism—vaginal delivery—thyroid crisis, Israel Kibel (by invitation) Discussion by H C Williamson ¶ Papers of the evening—a] Further studies in soft tissue diagnosis in pregnancy by L-rav, W Snow, Discussion by Paul Swenson, Presbyterian Hosp, b] An outbreak of impetigo Studies by the hospital epidemiologist, W Wolarsky (by invitation), Discussion by J Felson ¶ General discussion

Genito-Urinary Surgery, Medicine, Ophthalmology, Otolaryngology, Orthopedic Surgery—These Sections held no meeting in October because of conflict in dates with the Graduate Fortnight

IN MEMORIAM

LUDWIG KAST

With profound sorrow THE BULLETIN records the death of Ludwig Kast, honored Fellow of this Academy and devoted friend of medical education, who in the year 1927 proposed to the Committee on Medical Education of the Academy the institution of an annual graduate fortnight dedicated to the complete exposition of a chosen medical subject for the benefit of practitioners of medicine

We can conceive of no more fitting tribute to Doctor Kast than the publication of the following letter from his own hand

[LETTER FROM DR. LUDWIG KAST PROPOSING
INAUGURATION OF GRADUATE FORTNIGHTS TO
BE UNDERTAKEN BY THE NEW YORK ACADEMY
OF MEDICINE]

February 28, 1927

Doctor James F. McKernon,
Chairman, Committee on Medical Education,
New York Academy of Medicine
Dear Doctor McKernon

In the course of an investigation concerning the future development of Graduate Medical Education in New York, it has occurred to me that to the progressive efforts which the Academy has lately inaugurated, a new feature could be added which might be planned as follows:

A month is chosen during which all available opportunities in New York for lectures, demonstrations, symposiums, courses, ward rounds, operations are coordinated for the purpose of covering some big, outstanding problem of clinical nature from as many angles as possible. The underlying purpose would be to feature the topic by the very mass of contribution and by its quality so as to make it an event of national and later of international importance. After this has been accomplished a few times it will, as a matter of course, establish that month as a

standing feature of Medical Progress in New York.

1 *Time*—October or May would seem the months during which the largest number of physicians could be expected from out of town and also from within a radius of one hundred miles of New York. Between these two months the preference might be for October as those who would actively take part in this plan would be still refreshed from the summer.

For the first two weeks most of the important lectures and presentations could be planned, to be overlapped by two weeks more of courses and seminars and two or three important meetings toward the end of the month.

2 *Subject*—Some such problems as:
The Cancer problem
Infectious diseases and Problems of Immunity
Heart and Arteries
The problems of old age
The problems of ductless glands in Medicine and Surgery
Tuberculosis
Preoperative and postoperative management in abdominal surgery

- 3 *Program* (a) Special meetings at the Academy with symposium on the particularly debatable aspects of the problem
- (b) Cooperation if possible by the Harvey Society, Herter lectures, etc.
- (c) Meetings of the larger medical Societies in New York with papers pertaining to the chosen subject
- (d) Graduate courses at the medical colleges, Polyclinic, Post-Graduate, etc. Also Seminars on the subject
- (e) Outstanding authorities from Europe and from the Americas could be invited to read papers, particularly those who are already secured or to be secured for the Herter lectures, Harvey Society, etc
- (f) National societies, having for their object the advancement of the chosen subject might be induced to hold their annual meeting in New York during that month
- 4 *Preparations* It will, undoubtedly, take not less than half a year to make proper affiliations and coordinate the available

material and to publish the program, at least its outstanding papers and courses, well in advance

In arranging the program it might be well to have the graduate courses handle the simple, practical or didactic parts of the program and to reserve for the large meetings those parts which would lead to real debate particularly on the borderlines of the subject and its bearing upon Public Hygiene, and in general upon the needed cooperation between the medical profession and our Commonwealth. For this purpose the Academy might invite speakers from outside the medical profession

- 5 *Publication* It would seem possible to secure a nation-wide publicity well in advance without any expense.

The Academy, with or without cooperation of a publishing house, might undertake to publish a volume covering the important parts of the transactions

Sincerely yours,

L. KAST

DEATHS OF FELLOWS

BISHOP, LOUIS FAUGERES, SR 121 East 60 Street, New York City, born in New Brunswick, New Jersey, March 14, 1864, died in New York City, October 6, 1941, received his B A degree from Rutgers University in 1885 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1889, elected a Fellow of the Academy March 2, 1893, and served the Academy as Secretary from 1897 to 1903

Dr Bishop was consultant physician to the Lincoln Hospital, the Sea View Hospital and Goshen Hospital at Goshen, New York, director for the New York School for the Deaf, and instructor in graduate courses in internal medicine at Columbia University and Bellevue Hospital At one time he was professor of heart and circulatory diseases at Fordham University School of Medicine and consulting physician to the Mercy Hospital at Hempstead He was a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, a Fellow of the American Medical Association, past president of the American Therapeutic Society, a member of the National Gastroenterological Association, a member of the American Association of Pathologists and Bacteriologists and a member of the County and State Medical Societies

Dr Bishop was the author of "Heart Disease, Blood Pressure and the Nauheim Treatment," "Arteriosclerosis," "Heart Troubles, Their Prevention and Relief," "A Key to the Electrocardiograms," "A History of Cardiology," "Mechanism of the Heart and Its Anomalies," (translated from the French), and numerous articles

CONNELL, KARL Winton Lodge Branch, New York, born in Omaha, Nebraska, July 4, 1878, died in Scarsdale, New York, October 18, 1941, graduated in medicine from

the College of Physicians and Surgeons in 1900, elected a Fellow of the Academy, October 6, 1904

Dr Connell was professor of surgery at Creighton University, Omaha, from 1919 to 1924 As a Major in the A E F in France, Dr Connell won the Distinguished Service Medal by designing the first American gas mask He served as US Government observer in Germany and Austria in 1915 After the war he founded the Presbyterian Hospital at Omaha and was its president until 1924 He was a Fellow of the American College of Surgeons and a Fellow of the American Medical Association

GREGORY, MENAS SARRAS 115 East 61 Street, New York City, born in Morach, Turkey, July 14, 1872, died in Tuckahoe, New York, November 2, 1941, graduated in medicine from the Albany Medical College in 1898, elected a Fellow of the Academy December 3, 1908

Dr Gregory was director of the psychiatric department of Bellevue Hospital from 1904 to 1934 and consultant in psychiatry to that institution from 1936 until his death He was consultant in psychiatry to the New York Neurological Institute, a former professor of psychiatry at the New York Post-Graduate Medical School, and professor emeritus to the New York University College of Medicine He was a diplomate of the American Board of Psychiatry and Neurology, a Fellow of the American Medical Association, and a member of the American Psychiatric Association, the American Neurological Association, the Association for Research in Nervous and Mental Diseases, and the State and County Medical Societies

REGAUD, CLAUDE Paris, France born at Lyons, France, January 31, 1870, died at Couzon-au-Mont-d'Or, France, December 28, 1940, elected an Honorary Fellow of the Academy, November 8, 1934

Dr Regaud was professor at the Institut Pasteur, director of Laboratoire de Radiophysiology de l'Institut du Radium and of Service Thérapeutique de La Fondation Curie at Paris, a member of the Institut de France, a member of the Académie de

Médecine de Paris and an honorary member of the Académie Royale de Médecine de Belgique. During the World War he joined the Army with the rank of Captain in the Medical Corps and was promoted to the rank of *Médecin Commandant*. He was decorated with the Cross of the Légion d'Honneur and the Croix de Guerre.

Regaud and his school exerted an enormous influence on cancer research. Foreign governments and numerous institutions of both hemispheres turned to him for counsel. In 1924 he delivered an address at the 9th Annual Meeting of the American Radium Society in Chicago on "Some biological aspects of the radiation therapy of cancer," which was published in the *American Journal of Roentgenology*. In 1928 he was a delegate to the International Congress of Radiology, and in 1934 he was chosen to deliver the memorial address for Mme. Curie, at the Fondation Curie.

Dr. Regaud was the Editor of *Leçons de chirurgie de guerre* and the author of numerous studies, among which are "Traitement du cancer du col de l'utérus par les radiations" (1926), and "Comment on peut concevoir actuellement l'organisation de la lutte contre le cancer" (1929). Together with his collaborators, he published numerous works of which the *Archives de l'Institut du Radium*, a series of studies devoted to radiophysiology and radiotherapy, is regarded as a masterpiece.

SELTZ, SETH 17 East 96 Street, New York City, born in New York City, October 31, 1897, died in New York City, November 2, 1941. Graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1921, elected a Fellow of the Academy February 4, 1932.

Dr. Selig was attending orthopedic surgeon to the Montefiore and Mt. Sinai Hospitals, and a medical officer of the New York Fire Department. He was a diplomate of the American Board of Orthopedic Surgery, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Academy of Orthopedic Surgeons and a member of the State and County Medical Societies.

SHINE, FRANCIS WAYLES 116 East 62 Street, New York City, born in Orlando, Florida, June 25, 1875, died in Charlottesville, Virginia, September 24, 1941, graduated in medicine from the University of Virginia in 1898, elected a Fellow of the Academy May 5, 1910.

Dr. Shine was consulting surgeon to the New York Eye and Ear Infirmary and a member of its board of directors, consulting ophthalmologist to the New York Hospital, a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, and a member of the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, and the State and County Medical Societies.

Dr. Shine served in France as a Major with the American Expeditionary Force unit formed by the New York Hospital in 1917-18 and later served as consulting ophthalmologist for our Army in the Paris area.

WHEELWRIGHT, JOSEPH STORER 654 Madison Avenue, New York City, born in Bangor, Maine, November 23, 1875, died in Long Point, Ontario, Canada, October 9, 1941, received the degree of A.B. from Yale University in 1897, graduated in medicine from Cornell University Medical College in 1900, elected a Fellow of the Academy, January 7, 1926.

Dr. Wheelwright was founder and consulting surgeon to the Southampton Hospital at Long Island, and consulting surgeon to the Presbyterian Hospital in New York City. He was one of the founders of the Doctors Hospital, and, at the time of his death, was one of its directors and secretary of its medical board. At one time he also was connected with the Neurological Institute of New York and the East Maine General Hospital in Bangor. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

During the World War, Dr. Wheelwright served twice overseas, first as an executive of a French Army hospital unit and later as a Major in the Medical Corps of the American Expeditionary Force.

CITY OF NEW YORK
DEPARTMENT OF HEALTH
BUREAU OF RECORDS

125 WORTH STREET, NEW YORK, N. Y.

October 27, 1941

TO THE PRIVATE PRACTITIONERS OF MEDICINE AND SUPERINTENDENTS
OF CIVIL HOSPITALS IN THE CITY OF NEW YORK

Subject *New Procedure Regarding the Completion of Death Certificates*

Commencing November 1, 1941, private practitioners of medicine and civil hospital authorities will be relieved of the responsibility of completing the left side of death certificates required to be filed with the Department of Health, except in those instances where the body is unclaimed by a funeral director and is delivered to representatives of the City Mortuary for burial in the City Cemetery.

This procedure was adopted by the Board of Health, after approval by (1) the Public Health Relations Committee of the Academy of Medicine, (2) the Coordinating Council of the Five County Medical Societies, (3) the Greater New York Hospital Association, and (4) the Metropolitan Funeral Directors Association.

Funeral directors will hereafter be held responsible (1) for obtaining and entering the personal particulars required to complete items 2 to 14 of the death certificate, and (2) for obtaining the signature and address of the Informant, and relationship to the deceased in item 15. This change will bring procedures in New York City more nearly in conformity with practices in this regard elsewhere in the United States and will relieve physicians and hospital authorities, who frequently have little or no interest in this information, of this responsibility with which they were previously charged.

This means that, with the exception of City Cemetery cases—mentioned above—physicians and hospital authorities will be required only (1) to enter the name and social security account number of the deceased in item 1, (2) to complete the Medical Certificate of Death—items 16 to 21, inclusive, (and in Manhattan the Physician's Confidential Medical Report) and (3) to fill in the Physician's Supplementary Certificate of Death by Natural Causes—on the back of the certificate, or on a separate form, *except* in connection with Form 17-H-1941, used in Manhattan only (see upper left hand corner of certificate).

The Board of Health is confident that this change of procedure will receive unanimous approval and trusts that private practitioners and hospital authorities will renew their efforts to prepare *promptly, completely, and accurately*, the medical certificate of death and the related documents for which they are still responsible.

It would be appreciated if a copy of this letter could be posted on hospital bulletin boards where it will come to the attention of all attending and visiting physicians, as well as staff members.

THOMAS J. DUFFIELD,
Registrar of Records

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